201-14294B

3,3'-thiodipropionic acid, dioctadecyl ester

Id 693-36-7
Date 02/03/03

IUCLID

Data Set

Existing Chemical	:	ID: 693-36-7
CAS No.	:	693-36-7
EINECS Name	:	dioctadecyl 3,3'-thiodipropionate
EINECS No.	:	211-750-5
Molecular Weight	:	683.18
Molecular Formula	:	C42H82O4S

COMPANY INFORMATION

Name of Producer	:	Hampshire Chemical Corp., a wholly owned subsidiary of The Dow Chemical Company.
Street	:	45 Hayden Ave. Suite 2500
Town	:	Lexington, MA 02421-7994
Country	:	United States
Name of Producer	:	Cytec Industries Inc.
Street	:	5 Garret Mountain Plaza
Town	:	West Paterson, NJ 07424
Country	:	United States
Name of Producer	:	Crompton Corporation
Street	:	One American Lane
Town	:	Greenwich, CT 06831
Country	:	United States

1.1 GENERAL SUBSTANCE INFORMATION

Substance type	:	organic
Physical status	:	solid
Purity	:	>= 98 % w/w
Reliability	:	(2) valid with restrictions
Source	:	Dow Chemical Company MSDS for DISTEARYL THIODIPROPIONATE FLAKE

1.2 SYNONYMS

Propanoic acid, 3,3'-thiobis-, dioctadecyl ester (TSCA, DSL, ENCS, PICCS)
3,3'-Thiodipropionate de dioctadecyle (French) (DSL, EINECS)
dioctadecyl 3,3'-thiodipropionate (EINECS)
Dioctadecyl-3,3'-thiodipropionat (German) (EINECS)
3,3'-tiodipropionato de dioctadecilo (Spanish) (EINECS)
Propanoic acid, 3,3'-thiobis-, dioctadecyl ester (AICS)
3,3'-Thiobispropanoic acid dioctadecyl ester (ECL)
Propanoic acid, 3,3'-thiobis-, dioctadecyl ester (SWISS)
3,3'-THIODIPROPIONSAEURE-DISTEARYLESTER (German) (SWISS)
3,3'-THIODIPROPIONIC ACID, DISTEARYL ESTER (PICCS)
THIODIPROPIONIC ACID DIOCTADECYL ESTER (PICCS)
PROPANOATE, 3,3'-THIOBIS-, DIOCTADECYL (PICCS)
THIODIPROPIONATE, DISTEARYL (PICCS)

OTHER NAME(S):
Advastab 802
Advastab PS 802
Antage STDP-N
Antiox S
Antrage STDP-N
Arbestab DSTDP
beta,beta'-Thio-di (propionsaurestearylester)
Cyanox STDP
Dioctadecyl thiodipropionate
Dioctadecyl 3,3'-thiodipropionate
Distearyl b,b'-thiodipropionate
Distearyl b-thiodipropionate
Distearyl 3,3'-thiodipropionate
Distearyl thiodipropionate
DSTDP
DSTP
Evanstab 18

Hostanox SE 2
Hostanox SE 4
Hostanox VP-SE 2
IRGANOX PS 802
Lusmit SS
Naugard DSTDP
Plastanox STDP
Plastanox STDP Antioxidant
Propionic acid, 3,3'-thiodi-, dioctadecyl ester
PS 802
Seenox DS
Stearyl 3,3'-thiodipropionate
Sumilizer TPS
Thio 1
Varox DSTDP
Yoshinox DSTDP

1.3 IMPURITIES

CAS-No	:	112-92-5
EINECS-No	:	204-017-6
EINECS-Name	:	octadecan-1-ol
Contents	:	<= 2 % w/w
Reliability	:	(2) valid with restrictions
Reference	:	The Dow Chemical Company MSDS DISTEARYL THIODIPROPIONATE FLAKE

1.4 OCCUPATIONAL EXPOSURE LIMIT VALUES

Type of limit	:	MAK (DE)
Limit value	:	1.5 mg/m3
Remark	:	this is the limit for fine dust (reaching the alveoles)
Source	:	Ciba Additive GmbH Lampertheim Ciba Specialty Chemicals Inc. Basel Ciba Spezialitaetenchemie Lampertheim GmbH formerly CIBA Additive GmbH Lampertheim EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)

1.5 QUANTITY

Quantity	:	5 000 - 10 000 tonnes
Source	:	EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)

1.7 USE PATTERN

Type	:	type

Category	:	Use resulting in inclusion into or onto matrix
Source	:	EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
Type	:	industrial
Category	:	Polymers industry
Source	:	EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
Type	:	use
Category	:	Stabilizers
Source	:	EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
Type	:	use
Category	:	other: Antioxidans
Source	:	EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)

2.1 MELTING POINT

Value	:	**64 - 67 ° C**
Decomposition	:	no at ° C
Sublimation	:	no
Method	:	other
Year	:	1991
GLP	:	no
Test substance	:	
Source	:	Ciba Additive GmbH Lampertheim Ciba Specialty Chemicals Inc. Basel Ciba Spezialitaetenchemie Lampertheim GmbH formerly CIBA Additive GmbH Lampertheim EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
Reliability	:	Values from a collection of data are assigned a reliability code of 2g according to the criteria established by Klimisch *et al.* (1997).

2.2 BOILING POINT

Decomposition	:	300C
Method	:	
Year	:	
GLP	:	
Test substance	:	as prescribed by 1.1 - 1.4
Remark	:	**Decomposition temperature is 300C. Boiling point is >300C.**

2.3 DENSITY

Type	:	relative density
Value	:	**ca. .98 g/cm3 at 25° C**
Method	:	other
Year	:	
GLP	:	no data
Test substance	:	
Source	:	Ciba Additive GmbH Lampertheim Ciba Specialty Chemicals Inc. Basel Ciba Spezialitaetenchemie Lampertheim GmbH formerly CIBA Additive GmbH Lampertheim EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)

Reliability	:	Values from a collection of data are assigned a reliability code of 2g according to the criteria established by Klimisch *et al.* (1997).
Type	:	relative density
Value	:	**= 1.027 g/cm3 at 25° C**
Method	:	
Year	:	
GLP	:	no
Test substance	:	as prescribed by 1.1 - 1.4
Source	:	CYTEC MSDS (9/01/98). CYANOX STDP Antioxidant MSDS.
Reliability	:	Values from a collection of data are assigned a reliability code of 2g according to the criteria established by Klimisch *et al.* (1997).

2.4 VAPOUR PRESSURE

Value	:	**ca. 0.0000066 Pa at 20° C (4.95e-8 mmHg)**
Decomposition	:	Not reported
Method		other (measured)
Year	:	1985
GLP	:	no data
Test substance	:	
Source	:	Ciba Additive GmbH Lampertheim Ciba Specialty Chemicals Inc. Basel Ciba Spezialitaetenchemie Lampertheim GmbH formerly CIBA Additive GmbH Lampertheim EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
Reliability	:	Values from a collection of data are assigned a reliability code of 2g according to the criteria established by Klimisch *et al.* (1997).
Value	:	**= 8.98 e-13 mmHg at 25° C**
Decomposition	:	NA
Method		other (calculated): MPBPWIN version 1.40
Year	:	2001
GLP	:	Not applicable to estimations
Test substance	:	as prescribed by 1.1 - 1.4
Source	:	Estimated by the MPBPWIN Program (v.1.40), using Modified Grain Method. Syracuse Research Corporation, Syracuse, NY and U.S. Environmental Protection Agency, Office of Pollution Prevention and Toxics (2000)
Reliability	:	The vapor pressure determination from an accepted calculation method is assigned a reliability code of 2f according to the criteria established by Klimisch *et al.* (1997).

2.5 PARTITION COEFFICIENT

Log pow	:	**> 6 at 20° C**
Method		other (calculated)
Year	:	
GLP	:	Not applicable to estimations
Test substance	:	
Source	:	Ciba Additive GmbH Lampertheim Ciba Specialty Chemicals Inc. Basel Ciba Spezialitaetenchemie Lampertheim GmbH formerly CIBA Additive GmbH Lampertheim EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
Reliability	:	Values determined from an accepted calculation method are assigned a reliability code of 2g according to the criteria established by Klimisch *et al.* (1997).

Log pow	:	**= 17.68 at ° C**
Method		other (calculated): KOWWIN Program version 1.66
Year	:	2001
GLP	:	Not applicable to estimations
Test substance	:	as prescribed by 1.1 - 1.4
Source	:	Estimated by the KowWin Program (v.1.66) Syracuse Research Corporation, Syracuse, NY and U.S. Environmental Protection Agency, Office of Pollution Prevention and Toxics (2000)
Reliability	:	Values determined from an accepted calculation method are assigned a reliability code of 2g according to the criteria established by Klimisch *et al.* (1997).

2.6 WATER SOLUBILITY

Value	:	**< .001 g/l at 20 ° C**
Qualitative	:	not soluble
Pka	:	at 25 ° C
PH	:	ca. 6 at 10 g/l and 20 ° C
Method	:	Directive 84/449/EEC, A.6 "Water solubility"
Year	:	1989
GLP	:	no data
Test substance	:	
Remark	:	pH-value measured in a slurry
Source	:	Ciba Additive GmbH Lampertheim Ciba Specialty Chemicals Inc. Basel Ciba Spezialitaetenchemie Lampertheim GmbH formerly CIBA Additive GmbH Lampertheim

EUROPEAN COMMISSION - European Chemicals Bureau
Ispra (VA)

Reliability : Study assigned a reliability code of 2a according to the criteria established by Klimisch *et al.* (1997).

Value : **= 3.617e-14 mg/l at 25 ° C**
Qualitative :
Pka : at 25 ° C
PH : at and ° C
Method : other: (calculated) WSKOW version 1.40
Year : 2001
GLP : Not applicable to estimations
Test substance : as prescribed by 1.1 - 1.4
Remark : Log Kow used: 17.68 (estimated)
Source : Estimated from Kow with WSKOW (v1.40) : KowWin Estimate

Syracuse Research Corporation, Syracuse, NY and U.S. Environmental Protection Agency, Office of Pollution Prevention and Toxics (2000).

Reliability : Values determined from an accepted calculation method are assigned a reliability code of 2g according to the criteria established by Klimisch *et al.* (1997).

2.7 FLASH POINT

Value : = 257 ° C
Type : other
Method : other
Year : 1985
GLP : no data
Test substance :
Source : Ciba Additive GmbH Lampertheim
Ciba Specialty Chemicals Inc. Basel
Ciba Spezialitaetenchemie Lampertheim GmbH formerly CIBA Additive GmbH Lampertheim
EUROPEAN COMMISSION - European Chemicals Bureau
Ispra (VA)

Reliability : Values from a collection of data are assigned a reliability code of 2g according to the criteria established by Klimisch *et al.* (1997).

2.8 FLAMMABILITY

Result : non flammable
Method : other
Year :
GLP : no data
Test substance :
Source : Ciba Additive GmbH Lampertheim

Ciba Specialty Chemicals Inc. Basel
Ciba Spezialitaetenchemie Lampertheim GmbH formerly CIBA Additive GmbH Lampertheim
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)

Reliability : Values from a collection of data are assigned a reliability code of 2g according to the criteria established by Klimisch *et al.* (1997).

2.9 EXPLOSIVE PROPERTIES

Result : not explosive
Method : other
Year : 1990
GLP : no data
Test substance :
Source : Ciba Additive GmbH Lampertheim
Ciba Specialty Chemicals Inc. Basel
Ciba Spezialitaetenchemie Lampertheim GmbH formerly CIBA Additive GmbH Lampertheim
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
Reliability : Values from a collection of data are assigned a reliability code of 2g according to the criteria established by Klimisch *et al.* (1997).

2.10 OXIDIZING PROPERTIES

Result : no oxidizing properties
Source : Ciba Additive GmbH Lampertheim
Ciba Specialty Chemicals Inc. Basel
Ciba Spezialitaetenchemie Lampertheim GmbH formerly CIBA Additive GmbH Lampertheim
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
Reliability : Values from a collection of data are assigned a reliability code of 2g according to the criteria established by Klimisch *et al.* (1997).

3.1 PHOTODEGRADATION

Type	:	air
Light source	:	
Light spect.	:	nm
Rel. intensity	:	based on Intensity of Sunlight
Direct photolysis		
Halflife t1/2	:	**= 1.9 hour(s)**
		For reaction with hydroxyl radicals, the predicted half-life of the chemical is relatively rapid
Degradation	:	% after
Quantum yield	:	
Indirect photolysis		
Sensitizer	:	
Conc. of sens.	:	
Rate constant	:	**= 69.0337e-12 cm3/(molecule*sec)**
Degradation	:	% after
Deg. Product	:	
Method	:	other (calculated): AOP version 1.90
Year	:	2001
GLP	:	Not applicable to estimations
Test substance	:	as prescribed by 1.1 - 1.4
Source	:	Estimated by the AOP program (v1.90), which estimates rate constants and half-lives of atmospheric reactions of organic compounds with hydroxyl radicals and ozone in the atmosphere. Syracuse Research Corporation, Syracuse, NY and U.S. Environmental Protection Agency, Office of Pollution Prevention and Toxics (2000)
Reliability	:	Values determined from an accepted calculation method are assigned a reliability code of 2g according to the criteria established by Klimisch *et al.* (1997).

3.2 STABILITY IN WATER

Not Applicable: Due to Insolubility of Material.

3.3 TRANSPORT BETWEEN ENVIRONMENTAL COMPARTMENTS

MacKay Level III Fugacity Model

Medium	Concentration %	Emissions (kg/hr)
Air	**0.0885**	**1000**
Water	**3.39**	**1000**
Soil	**29.1**	**1000**
Sediment	**67.4**	**0**

Persistence Time	1.66e+3 hr

Medium	Concentration %	Emissions (kg/hr)
Air	**2.15**	**1000**
Water	**1.08**	**0**
Soil	**75.4**	**0**
Sediment	**21.4**	**0**
Persistence Time		**205 hr**

Medium	Concentration %	Emissions (kg/hr)
Air	**2.14e-14**	**0**
Water	**4.79**	**1000**
Soil	**7.51e-13**	**0**
Sediment	**95.2**	**0**
Persistence Time		**3.48e+3 hr**

Medium	Concentration %	Emissions (kg/hr)
Air	**2.59e-17**	**0**
Water	**1.67e-3**	**0**
Soil	**100**	**1000**
Sediment	**3.32e-2**	**0**
Persistence Time		**1.3e+3 hr**

Reference : Estimated by the Level III Fugacity Model (Full-Output)

Syracuse Research Corporation, Syracuse, NY and U.S. Environmental Protection Agency, Office of Pollution Prevention and Toxics (2000).

Reliability : Values determined from an accepted calculation method are assigned a reliability code of 2g according to the criteria established by Klimisch *et al.* (1997).

3.4 BIODEGRADATION

Type : Aerobic
Inoculum : Bacteria collected from activated sludge of the sewage treatment plant of CH – 4153 Reinach on 2/6/89.
Contact time : 28 days
Degradation : = 15 % after 28 day (11.3 mg test substance/L)
= 2 % after 28 day (23.9 mg test substance/L)
Result : **Not Readily Biodegradable**

Method : OECD Guide-line 301 B "Ready Biodegradability: Modified Sturm Test (CO2 evolution)"

- 2-liter flasks equipped with gas inlet and magnetic stirrers were used as the test vessels. The test medium was prepared according to the method described in the guideline. The temperature was maintained at 22 ± 2 °C, 28 days. Aeration consisted of ~ 25 ml/min air free of carbon dioxide.
- Reference Substance: 20 mg/L with 0.5 ml of the nonylphenol 10EO5PO.
- Test Substance: 11.3 mg/L and 23.9 mg/L
- 1200 ml of the mineral solution with the inoculum was aerated for 24 hours in the test vessel. In 300 ml mineral solution 0.5 ml nonylphenol 10EO5PO (solution of 30 mg in 100 ml bidist. Water) and 16.3 rsp. 29.9 mg of test substance were added and homogenized. This solution was given to the test vessel which was immediately connected to the CO2 traps.
- Blank: Water as specified in the guideline containing 0.5 ml of the nonylphenol 10EO5PO solution.
- Measurements: Determination of the initial CO2 of the 0.05 N sodium hydroxide and the CO2, absorbed in the absorbers filled with 200 ml 0.05 N sodium hydroxide on the days 7, 10, 13, 17, 20, 24, 27, and 28.
- The biodegradation was calculated on the basis of the theoretical carbon content of the test substance and the cumulative quantities of carbon dioxide determined on the days of measurements. For the calculation the formula given in the guideline was used.
- Reference Substance Biodegradation: 20 mg/L = 92.2% in 28 days.
- Test Substance: 11.3 mg/L = 15% in 28 days & 23.9 mg/L = 2% in 28 days.

Year : 1989
GLP : In spirit of GLP
Test substance : as prescribed by 1.1 - 1.4
Remark : Due to the poor solubility of the test material in water, an emulsifier was used to achieve a better distribution in the

medium. The test substance was added to the medium, homogenized with nonylphenol 10EO5PO.

The volume of the test solution was reduced from 3L to 1.5L. The CO2 formed by biodegradation was absorbed with NaOH and determined on a carbon analyzer.

Source : Report on the Test for Ready Biodegradability of TK10594 in the Modified Sturm Test, Ciba-Geigy Ltd. Basle, Switzerland. April 4, 1989.

Reliability This study is assigned a reliability code of 1b according to the criteria established by Klimisch et al. (1997). It was conducted under OECD guidelines.

Type : aerobic
Inoculum :
Contact time : 28 day
Degradation : **= 0 % after 28 day**
Result : **Not Readily Biodegradable**
Deg. Product : NA
Method : OECD Guide-line 301 B "Ready Biodegradability: Modified Sturm Test (CO2 evolution)"
Year : 1985
GLP : No data
Test substance : as prescribed by 1.1 - 1.4
Remark : Results are the average of testing done at two separate testing facilities in a series of round robin tests to compare the results of various ready biodegradability tests.

Result : There was 0% degradation attained in 28 days in 2 separate Sturm tests.

Source Blok, J., de Morsier, AA., Gerike, P., Reynolds, L. and Wellens, H. (1985). Harmonisation of ready biodegradability tests. Chemosphere 14:1805-1820.

Reliability This study is assigned a reliability code of 1d according to the criteria established by Klimisch et al. (1997). It was conducted under OECD guidelines.

Type : aerobic
Inoculum :
Contact time : 28 day
Degradation : **= Average 40 % after 28 day**
Result : **Not Readily Biodegradable**
Deg. Product : NA
Method : OECD Guide-line 301 C "Ready Biodegradability: Modified MITI Test (I)"
Year : 1980
GLP : No data

Test substance	:	
Remark	:	Results are the average of testing done at five separate testing facilities in a series of round robin tests to compare the results of various ready biodegradability tests.
Result	:	40% degradation was attained in 28 days in 5 separate MITI I tests.
Flag	:	Critical study for SIDS endpoint
Source	:	Blok, J., de Morsier, AA., Gerike, P., Reynolds, L. and Wellens, H. (1985). Harmonisation of ready biodegradability tests. Chemosphere 14:1805-1820.
Reliability		This study is assigned a reliability code of 1d according to the criteria established by Klimisch et al. (1997). It was conducted under OECD guidelines.
Type	:	aerobic
Inoculum	:	
Contact time	:	30 days
Degradation	:	**= 0 % after 30 day**
Result	:	**Not Readily Biodegradable**
Deg. Product	:	NA
Method	:	OECD Guide-line 301 D "Ready Biodegradability: Closed Bottle Test"
Year	:	1980
GLP	:	No data
Test substance	:	as prescribed by 1.1 - 1.4
Source	:	Blok, J., de Morsier, AA., Gerike, P., Reynolds, L. and Wellens, H. (1985). Harmonisation of ready biodegradability tests. Chemosphere 14:1805-1820.
Reliability		This study is assigned a reliability code of 1a according to the criteria established by Klimisch et al. (1997). It was conducted under OECD guidelines.
Type	:	aerobic
Inoculum	:	
Contact time	:	
Degradation	:	**= 60 %**
Result	:	**Inherently Biodegradable**
Deg. Product	:	NA
Method	:	OECD Guide-line 302 C "Inherent Biodegradability: Modified MITI Test (II)"
Year	:	1980
GLP	:	No data
Test substance	:	as prescribed by 1.1 - 1.4
Remark	:	Results are the average of testing done at five separate testing facililties in a series of round robin tests to compare the results

	of various inherently biodegradeability tests.
Source	Blok, J., de Morsier, AA., Gerike, P., Reynolds, L. and Wellens, H. (1985). Harmonisation of ready biodegradability tests. Chemosphere 14:1805-1820.
Reliability	This study is assigned a reliability code of 1d according to the criteria established by Klimisch et al. (1997). It was conducted under OECD guidelines.

3.6 BOD5, COD OR BOD5/COD RATIO

Method	:	Directive 84/449/EEC, C.9 "Biodegradation: Chemical Oxygen Demand"
GLP	:	no data
COD	:	ca. 2000 mg/g substance
Source	:	Ciba Additive GmbH Lampertheim Ciba Specialty Chemicals Inc. Basel Ciba Spezialitaetenchemie Lampertheim GmbH formerly CIBA Additive GmbH Lampertheim EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
Reliability		This study is assigned a reliability code of 2a according to the criteria established by Klimisch et al. (1997). It was conducted under EU Directive guidelines.

4.1 ACUTE/PROLONGED TOXICITY TO FISH

Type	:	OECD Guideline 203
Species	:	Zebra-Fish (Brachydanio rerio)
Exposure period	:	96 hour(s)
Unit	:	mg/l
Analytical monitoring	:	no
LC50	:	**>100 mg/L**
Method	:	10 fishes per concentration and control, 10 fish per aquarium. The fish were ~25mm in length, 0.13 g. The fish were not fed for 24 hours prior to exposure. The Glass aquaria were 20L capacity with 15 L dechlorinated tap water, hardness 171 mg CaCO3/L, temperature 23 ± 1°C. The aquaria were gently aerated during the test; the fish were provided fluorescent lighting 16 hours daily. Oxygen, pH, and temperature were measure daily. The nominal test concentrations were 10, 18, 32, 58, and 100 mg/L. Test material was added to the water prior to transfer in of the fish. A slight deposit was observed at conc. 10-100 mg/L after 48 hours of exposure. Due to the poor solubility of the test material in water, the test substance and 4 mg/L alkylphenol-polyglycolether was added directly to the water in the tanks. None of the fish died in any of the test vessels and there were no signs of altered swimming behavior, loss of equilibrium, respiratory effects, exopthalmus or pigmentation changes.
Year	:	1989
GLP	:	In spirit of GLP
Test substance	:	as prescribed by 1.1 - 1.4
Remark	:	96Hr LC50 is equivalent to highest concentration tested; thus value may be higher than reported.
Source	:	Report on the Test for Acute Toxicity of IRGANOX PS 802 to Zebra-Fish, Ciba-Geigy Ltd. Basle, Switzerland. January 9, 1989.
Reliability		This study is assigned a reliability code of 1b according to the criteria established by Klimisch et al. (1997). It was conducted under OECD guidelines.

4.2 ACUTE TOXICITY TO AQUATIC INVERTEBRATES

Type	:	OECD Guideline 202
Species	:	Daphnia Magna Straus 1820
Exposure period	:	48 hour(s)

Unit	:	mg/l
Analytical monitoring	:	No
EC0	:	= 180
EC50	:	**= 780 mg/l**
EC100	:	> 1000
Method	:	20 daphnia per concentration and control, 4 replicates of 5 daphnia each. The daphnia were not fed during the test. The daphnia were obtained from in-house cultures at Ciba-Geigy Ltd., Basle, Switzerland. The water was reconstituted water prepared in a 1000 ml beaker; total hardness was 240 mg CaCO3/L. The water was aerated with clean air for at least 24 hrs before use. The daphnia were placed in 100 ml solution per beaker, covered with watch glasses. The temperature was maintained at 20 ± 1°C, 16 hours fluorescent lighting daily. Oxygen, pH, and temperature were checked at the start of the test. Due to the poor solubility of the test material in water, a stock solution of 1 g of the test substance and 4 mg alkylphenol-polyglycolether were mixed and dissolved in 1000 ml water. Control = Water plus 4 mg alkylphenol-polyglycol ether per liter water in the concentration used for the highest test concentration. Nominal test concentrations were 100, 180, 320, 580, and 1000 mg/L. Test material was added to the water prior to transfer in of the daphnia. A slight deposit was observed at all concentrations. The EC0 was determined to be 780 mg/L and the EC100 was determined to be >1000 mg/L.
Year	:	1988
GLP	:	In spirit of GLP
Test substance	:	as prescribed by 1.1 - 1.4
Remark	:	None
Source		Report on the Test for Acute Toxicity of TK10594 to Daphnia Magna, Ciba-Geigy Ltd. Basle, Switzerland. December 16, 1988.
Reliability		This study is assigned a reliability code of 1b according to the criteria established by Klimisch et al. (1997). It was conducted under OECD guidelines.

4.3 TOXICITY TO AQUATIC PLANTS E.G. ALGAE

Species	:	Green Algae (Scenedesmus subspicatus)
Type	:	87/302/EEC Algae Growth Inhibition Test

Endpoint	:	biomass
Exposure period	:	72 hour(s)
Unit	:	mg/l
Analytical monitoring	:	Values based on nominal concentrations
EbC50	:	**60 mg/L**
NOEbC (0-72 h)	:	3.7 mg/L
Method	:	100 ml Erlenmeyer flasks with 50 ml test solution per flask were used. The temperature was maintained at 23 ± 1°C. Lighting was continuous cold white fluorescent light, 109 uE/m2 sec ± 20 %. Stock solution was prepared using 2.0 g test substance, 2.0 g water containing 0.4% Lecithin and 4 g water, mixed together and then blended with 12 g water (this blend contains 10% test substance). 1 ml of the blend was mixed and made up to 1000 ml water, achieving 100 mg/L test substance and 0.4 mg/L vehicle. Test concentrations were nominal determined to be 1.23, 3.7, 11, 33, and 100 mg/L. The vehicle was 0.4 mg Lecithin/L. Water was used as the blank. Each test concentration was tested in 3 replicates, the blank control in 6. Calculated amounts of the stock solution to produce the desired test concentrations were given into the water and were homogeneously distributed. The algae were then transferred into the flasks. Small parts of the test substance were swimming on the surface of the test water at all concentrations and a small deposit was observed at the test concentration of 100 mg/L. Cell densities were measured at 24, 48, and 72 hours exposure on a TOA cell counter. Temperature was continuously measured and maintained at 23 ± 1°C. pH was measured at 0h and 72h exposure. The EbC 50 (0-72 h) = 60 mg/L 95% CL 32-127 mg/L. The NOEbC (0-72 h) (5% level = 3.7 mg/L).
Year	:	1992
GLP	:	In spirit of GLP
Test substance	:	as prescribed by 1.1 - 1.4
Remark	:	Values based on nominal concentrations.
Source		Report on the Growth Inhibition Test of IRGANOX PS 802 to Green Algae (Scenedesmus subspicatus), Ciba-Geigy Ltd. Basle, Switzerland. December 17, 1992.
Reliability		This study is assigned a reliability code of 1b according to the

criteria established by Klimisch et al. (1997). It was conducted under OECD guidelines.

4.4 TOXICITY TO MICROORGANISMS E.G. BACTERIA

Type	:	aquatic
Species	:	activated sludge
Exposure period	:	3 hour(s)
Unit	:	mg/l
Analytical monitoring	:	yes
EC50	:	**> 100 mg/L**
EC20	:	> 100 mg/L
EC80	:	> 100 mg/L
Method	:	OECD Guide-line 209 "Activated Sludge, Respiration Inhibition Test"
Year	:	1984
GLP	:	no data
Test substance	:	as prescribed by 1.1 - 1.4
Source	:	Ciba Additive GmbH Lampertheim Ciba Specialty Chemicals Inc. Basel Ciba Spezialitaetenchemie Lampertheim GmbH formerly CIBA Additive GmbH Lampertheim EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
Reliability		This study is assigned a reliability code of 1b according to the criteria established by Klimisch et al. (1997). It was conducted under OECD guidelines.

5.1.1 ACUTE ORAL TOXICITY

Type	:	LD50
Species	:	rat
Strain	:	
Sex	:	
Number of animals	:	
Vehicle	:	
Value	:	**> 5000 mg/kg bw**
Method	:	other
Year	:	1975
GLP	:	no data
Test substance	:	as prescribed by 1.1 - 1.4
Source	:	Ciba Additive GmbH Lampertheim Ciba Specialty Chemicals Inc. Basel Ciba Spezialitaetenchemie Lampertheim GmbH formerly CIBA Additive GmbH Lampertheim EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
Reliability	:	This study is assigned a reliability code of 2e according to the criteria established by Klimisch *et al.* (1997). It was not conducted under GLP or OECD guidelines but generally meets scientific standards, is well documented and is accepted for assessment.

Type	:	LD50
Species	:	rat
Strain	:	
Sex	:	male
Number of animals	:	
Vehicle	:	other: corn oil
Value	:	**> 2000 mg/kg bw**
Method	:	
Year	:	1975
GLP	:	no
Test substance	:	as prescribed by 1.1 - 1.4
Method	:	Test material administered as a 10% suspension in corn oil. Groups of three rats/dose level were dosed with 0.126, 0.252, 0.5, 1.0 or 2.0 mg/kg. Animals were fasted overnight prior to dosing. One of the three animals in each dose level was necropsied 24 hours after administration of the test material. The remaining two animals in each dose level were sacrificed 14 days post-dosing.
Result	:	All animals survived dose levels as high as 2000 mg/kg. Animals gained weight and appeared to be normal throughout the two week recovery period. The 2000 mg/kg rat necropsied 24 hours post-dosing had a roughened, moist hair coat but no

other effects were visible.

Source : Keeler, P.A. and Olson, K.J. (1975). Toxicological properties and industrial handling hazards of distearyl thiodipropionate. Unpublished report of The Dow Chemical Company.

Reliability : This study is assigned a reliability code of 2e according to the criteria established by Klimisch *et al.* (1997). It was not conducted under GLP or OECD guidelines but generally meets scientific standards, is well documented and is accepted for assessment.

Type : LD50
Species : rat
Strain :
Sex :
Number of animals :
Vehicle : other: olive oil
Value : **> 2500 mg/kg bw**
Method :
Year : 1947
GLP : no
Test substance : no data
Remark : Groups of 5 and 12 rats received 2000 and 2500 mg/kg distearyl thiodipropionate, respectively, dissolved in olive oil. After dosing, animals were observed for one week prior to necropsy.
Remark: : No additional information could be gleaned from the report.
Result : Oral LD50 greater than 2500 mg/kg in rats.

One of 12 rats died two days after receiving 2500 mg/kg. All other animals survived.

Sources : AFREAW Advances in Food Research (1951). Academic Press, Inc., 1 E. Fist St., Duluth, MN 55802 V3:197.

: Tullar, P.E. (1947). The pharmacology and toxicology of thiodipropionic acid and its dilauryl and distearyl esters. Final Report. The Kalusowski Memorial Research Laboratories, School of Pharmacy, The George Washington University, Washington, D.C. Unpublished data. FDA FOIA request #F88-8055. Document #001974-002031.

Reliability : This study is assigned a reliability code of 2e according to the criteria established by Klimisch *et al.* (1997). It was not conducted under GLP or OECD guidelines but generally meets scientific standards, is well documented and is accepted for assessment.

Type : LD50
Species : mouse
Strain :

Sex	:	
Number of animals	:	
Vehicle	:	other: olive oil
Value	:	> 2000 mg/kg bw
Method	:	
Year	:	1947
GLP	:	no
Test substance	:	no data
Remark	:	Groups of 10 mice received 300 or 500 mg/kg orally of distearyl thiodipropionate dissolved in olive oil. Two additional groups of 18 and 20 mice received 2000 mg/kg orally of the same material. No additional information could be gleaned from the report.
Result	:	Greater than 2000 mg/kg in mice. One of ten animals receiving 300 mg/kg, 1 of 18 receiving 2000 mg/kg and 4 of 20 receiving 2000 mg/kg died. There were no characteristic acute symptoms. No other information supplied.
Sources	:	AFREAW Advances in Food Research (1951). Academic Press, Inc., 1 E. Fist St., Duluth, MN 55802 V3:197.
	:	Tullar, P.E. (1947). The pharmacology and toxicology of thiodipropionic acid and its dilauryl and distearyl esters. Final Report. The Kalusowski Memorial Research Laboratories, School of Pharmacy, The George Washington University, Washington, D.C. Unpublished data. FDA FOIA request #F88-8055. Document #001974-002031.
Reliability	:	This study is assigned a reliability code of 2e according to the criteria established by Klimisch *et al.* (1997). It was not conducted under GLP or OECD guidelines but generally meets scientific standards, is well documented and is accepted for assessment.

5.1.3 ACUTE DERMAL TOXICITY

Type	:	LD50
Species	:	rat
Strain	:	
Sex	:	
Number of animals	:	
Vehicle	:	
Value	:	> 2000
Method	:	OECD Guide-line 402 "Acute dermal Toxicity"
Year	:	1987
GLP	:	yes

Test substance	:	as prescribed by 1.1 - 1.4
Source	:	Ciba Additive GmbH Lampertheim Ciba Specialty Chemicals Inc. Basel Ciba Spezialitaetenchemie Lampertheim GmbH formerly CIBA Additive GmbH Lampertheim EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
Reliability	:	This study is assigned a reliability code of 2a according to the criteria established by Klimisch *et al.* (1997). It was conducted under OECD guidelines but documentation is limited.

5.1.4 ACUTE TOXICITY, OTHER ROUTES

Type	:	LD50
Species	:	mouse
Strain	:	
Sex	:	
Number of animals	:	
Vehicle	:	
Route of admin.	:	i.p.
Exposure time	:	
Value	:	> 2000 - mg/kg bw
Method	:	
Year	:	1951
GLP	:	no
Test substance	:	other TS
Remark	:	The test substance is not exactly specified, described as Distearyl ester of Thiodipropionic acid
Source	:	Ciba Additive GmbH Lampertheim Ciba Specialty Chemicals Inc. Basel Ciba Spezialitaetenchemie Lampertheim GmbH formerly CIBA Additive GmbH Lampertheim EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA) AFREAW Advances in Food Research (1951). Academic Press, Inc., 1 E. Fist St., Duluth, MN 55802 V3:197.
Reliability	:	This study is assigned a reliability code of 3c according to the criteria established by Klimisch *et al.* (1997). Unsuitable test system.

5.2.1 SKIN IRRITATION

Species	:	rabbit
Concentration	:	
Exposure	:	
Exposure time	:	
Number of animals	:	

PDII	:	
Result	:	slightly irritating
EC classification	:	not irritating
Method	:	other
Year	:	1965
GLP	:	no data
Test substance	:	as prescribed by 1.1 - 1.4
Remark	:	Test method according to the method given in the ~Hazardous Substances Regulations~ under the U.S.Federal Hazardous Substances Labelling Act Sect. 191.11 (February 1965).
Source	:	Ciba Additive GmbH Lampertheim Ciba Specialty Chemicals Inc. Basel Ciba Spezialitaetenchemie Lampertheim GmbH formerly CIBA Additive GmbH Lampertheim EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
Reliability	:	This study is assigned a reliability code of 2a according to the criteria established by Klimisch *et al.* (1997). It was conducted under FHSA guidelines but documentation is limited.
Species	:	rabbit
Concentration	:	
Exposure	:	
Exposure time	:	
Number of animals	:	
PDII	:	
Result	:	
EC classification	:	
Method	:	
Year	:	1975
GLP	:	no
Test substance	:	no data
Method	:	White laboratory rabbits were shaved and then rested for several days to allow any abrasions to heal completely and to be sure skin is suitable for use. INTACT ABDOMEN: Dry test material was applied under a 1 inch by 1 inch cotton pad held in place by a cloth bandage taped to the hair. Ten applications were made over a period of 14 days. This allows continuous intimate contact with the skin for a two week period. ABRADED ABDOMEN: An area of skin about 1 inch by 1 inch was cross-hatched with a sharp hypodermic needle to penetrate the stratum corneum but not to produce more than a trace of bleeding. Dry test material was applied under a 1 inch by 1 inch cotton pad held in place by a cloth bandage taped to the hair. Three consecutive daily applications were made

which allows for 3 days of intimate, confined contact with the abraded skin.

Each site was graded 24 hours post-dosing and 3 and 10 days after the last application to the intact skin. The abraded skin was examined everytime the intact skin was examined. Parameters graded on intact and abraded skin include redness, edema, necrosis, exfoliation, hair loss, scabs or scars.

Result : After the third application, questionable redness was noted on the intact skin. There were no other effects noted in the intact skin through 10 applications or on abraded skin through 3 applications.

Source : Keeler, P.A. and Olson, K.J. (1975). Toxicological properties and industrial handling hazards of distearyl thiodipropionate. Unpublished report of The Dow Chemical Company.

Reliability : This study is assigned a reliability code of 2e according to the criteria established by Klimisch *et al.* (1997). It was not conducted under GLP or OECD guidelines but generally meets scientific standards, is well documented and is accepted for assessment.

Species : rabbit
Concentration :
Exposure :
Exposure time :
Number of animals :
PDII :
Result :
EC classification :
Method :
Year : 1975
GLP : no
Test substance : no data
Method : White laboratory rabbits were shaved and then rested for several days to allow any abrasions to heal completely and to be sure skin is suitable for use.

INTACT ABDOMEN: A solution containing test material was applied under a 1 inch by 1 inch cotton pad held in place by a cloth bandage taped to the hair. Ten applications were made over a period of 14 days. This allows continuous intimate contact with the skin for a two week period.

ABRADED ABDOMEN: An area of skin about 1 inch by 1 inch was cross-hatched with a sharp hypodermic needle to

penetrate the stratum corneum but not to produce more than a trace of bleeding. A solution containing test material was applied under a 1 inch by 1 inch cotton pad held in place by a cloth bandage taped to the hair. Three consecutive daily applications were made which allows for 3 days of intimate, confined contact with the abraded skin.

Each site was graded 24 hours post-dosing and 3 and 10 days after the last application to the intact skin. The abraded skin was examined everytime the intact skin was examined. Parameters graded on intact and abraded skin include redness, edema, necrosis, exfoliation, hair loss, scabs or scars.

Result : The solution containing test material was not irritating to intact or abraded skin throughout the study.

Source Keeler, P.A. and Olson, K.J. (1975). Toxicological properties and industrial handling hazards of distearyl thiodipropionate. Unpublished report of The Dow Chemical Company.

Reliability : This study is assigned a reliability code of 2e according to the criteria established by Klimisch *et al.* (1997). It was not conducted under GLP or OECD guidelines but generally meets scientific standards, is well documented and is accepted for assessment.

Species : rabbit
Concentration :
Exposure :
Exposure time : 24 hour(s)
Number of animals :
PDII :
Result : not irritating
EC classification :
Method :
Year : 1947
GLP : no
Test substance : as prescribed by 1.1 - 1.4
Remark : The area on the back was closely clipped and the ester was applied to a particular area by means of a sterile gauze covering held in place with adhesive tape for 24 hours. Observations were made at 24-, 48- and 72-hour intervals. Particular attention was paid to redness, inflammation or other signs of irritation. The animals were prevented from disturbing the patches by being comfortably restrained in carefully designed racks.

Olive oil was used for dissolving the distearyl ester (50 mg/cc).

Result	:	None of the tests showed redness or other signs of irritation.
Source	:	Tullar, P.E. (1947). The pharmacology and toxicology of thiodipropionic acid and its dilauryl and distearyl esters. Final Report. The Kalusowski Memorial Research Laboratories, School of Pharmacy, The George Washington University, Washington, D.C. Unpublished data. FDA FOIA request #F88-8055. Document #001974-002031.
Reliability	:	This study is assigned a reliability code of 2e according to the criteria established by Klimisch *et al.* (1997). It was not conducted under GLP or OECD guidelines but generally meets scientific standards, is well documented and is accepted for assessment.

5.2.2 EYE IRRITATION

Species	:	rabbit
Concentration	:	
Dose	:	
Exposure Time	:	
Comment	:	
Number of animals	:	
Result	:	slightly irritating
EC classification	:	not irritating
Method	:	other
Year	:	1965
GLP	:	no
Test substance	:	as prescribed by 1.1 - 1.4
Remark	:	Test method according to the procedure set out in the ~Hazardous Substances Regulations~ under the U.S. Federal Hazardous Substances Labelling Act Sect. 191.12 (February 1965).
Source	:	Ciba Additive GmbH Lampertheim Ciba Specialty Chemicals Inc. Basel Ciba Spezialitaetenchemie Lampertheim GmbH formerly CIBA Additive GmbH Lampertheim EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
Reliability	:	This study is assigned a reliability code of 2a according to the criteria established by Klimisch *et al.* (1997). It was conducted under FHSA guidelines but documentation is limited.

Species	:	rabbit
Concentration	:	
Dose	:	
Exposure Time	:	
Comment	:	

Number of animals	:	
Result	:	
EC classification	:	
Method	:	
Year	:	1975
GLP	:	no
Test substance	:	no data

Method : Prior to conducting the test, both eyes of a rabbit were stained with fluorescein for any evidence of injury. A rest period of at least 24 hours occurred prior to introducing test material into the eye.

The test material was applied to both the right and left eye of one male rabbit. Thirty seconds after applying the test material to the right eye, the eye was washed for 2 minutes in a flowing stream of tepid water. The left eye was not washed.

Both eyes were observed immediately for pain. Within 2-3 minutes after the unwashed eye was treated, each was observed for conjunctival and corneal response. Similar observations were made of both eyes at 1 hour, 24 hours, 48 hours and 7 days after treatment. Note that both eyes were stained at 1, 24 and 48 hours and 7 days. This necessitated washing both eyes to remove excessive stain.

Result : Very slight pain and conjunctival irritation were noted in both eyes immediately after application of the test material. There was no evidence of corneal injury in either washed or unwashed eye. Similarly, there was no evidence of conjunctival irritation or corneal effects in either washed or unwashed eyes after 1, 24 or 48 hours or 7 days post-exposure.

Source Keeler, P.A. and Olson, K.J. (1975). Toxicological properties and industrial handling hazards of distearyl thiodipropionate. Unpublished report of The Dow Chemical Company.

Reliability : This study is assigned a reliability code of 2e according to the criteria established by Klimisch *et al.* (1997). It was not conducted under GLP or OECD guidelines but generally meets scientific standards, is well documented and is accepted for assessment.

5.3 SENSITIZATION

Type	:	Guinea pig maximization test
Species	:	guinea pig
Number of animals	:	
Vehicle	:	

Result	:	not sensitizing
Classification	:	not sensitizing
Method	:	Directive 84/449/EEC, B.6 "Acute toxicity (skin sensitization)"
Year	:	1984
GLP	:	yes
Test substance	:	as prescribed by 1.1 - 1.4
Source	:	Ciba Additive GmbH Lampertheim Ciba Specialty Chemicals Inc. Basel Ciba Spezialitaetenchemie Lampertheim GmbH formerly CIBA Additive GmbH Lampertheim EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
Reliability	:	This study is assigned a reliability code of 2a according to the criteria established by Klimisch *et al.* (1997). It was conducted under EU guidelines but documentation is limited.

5.4 REPEATED DOSE TOXICITY

Species	:	rat
Sex	:	male
Strain	:	
Route of admin.	:	oral feed
Exposure period	:	Phase 1:292 days Phase 2: Continuation out to 2 years
Frequency of treatment	:	daily
Post obs. period	:	
Doses	:	0, 0.5, or 3.0 % in the diet
Control group	:	yes
Method	:	
Year	:	1947
GLP	:	no
Test substance	:	as prescribed by 1.1 - 1.4
Method	:	Groups of 10 male rats received diets containing 0, 0.5 or 3.0% distearyl thiodipropionate for 292 days. Body weights, feed consumption, mortalities and general appearance were recorded on a weekly basis. Gross pathology was performed on animals that died. Four months after the study started, some animals developed enteritis which was accompanied by weight loss and a few deaths. Zero of ten controls died, two of ten from the 0.5% group died and 5 of ten from the 3.0% group died. Subsequently these rats were continued on their specific feedings for a period of more than two years. Body weights and mortalities were recorded.
Remark	:	Table 7 of the report refers to 11 animals in the control group

and two control animals surviving until the end of the study. This does not agree with the text and Table 6.

Result : As mentioned in the Methods section, higher mortality was noted in the distearylthiodipropionate groups with 2 low dose and 5 high dose animals dying due to enteritis. In addition, two, one and two deaths were observed in the control, 0.5 and 3.0% groups which were attributed to "feeding" during the first six months of the study. The authors concluded that this material is "relatively non-toxic in concentrations up to 3.0% in the daily food of rats over a six-month period."

The survivors remained on test for 2 years. At the end of the two years, each of the control, 0.5 and 3.0% groups had one animal surviving.

Source : Ciba Additive GmbH Lampertheim
Ciba Specialty Chemicals Inc. Basel
Ciba Spezialitaetenchemie Lampertheim GmbH formerly CIBA Additive GmbH Lampertheim
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)

Reliability : This study is assigned a reliability code of 3a according to the criteria established by Klimisch *et al.* (1997). Documentation is insufficient.

Species : rat
Sex : male
Strain :
Route of admin. : oral feed
Exposure period : 2 years
Frequency of treatment : daily
Post obs. period :
Doses : 0, 0.5, 1.0 or 3.0%
Control group : yes
Result : **NOAEL = 3.0% dietary level**
Year : 1947
GLP : no
Test substance : as prescribed by 1.1 - 1.4
Method : Groups of 20 rats received diets containing 0, 0.5, 1.0 or 3.0% distearyl thiodipropionate for two years. Body weights, feed consumption, mortalities and general appearance were recorded on a monthly basis. Gross pathology was performed on animals that died. Specific sex of animals on test unstated.
Remark : The study by Tullar conducted between 1944 and 1947 did not supply sufficient information to accurately convert percentage

test material in the feed to mg/kg/day as routinely used today. The only information supplied by Tullar was the average feed consumed/rat/day (19,800 mg/rat/day) for the entire study and the average weight at selected time points. The highest average body weight for the group receiving 3% in the diet was 390 grams. If one uses these two values, the value would be 1523 mg/kg/day. However, the use of the average feed consumption for the entire study may not be appropriate.

Thus, rather than report this value in the test plan, control data from representative studies with F-344 rats of 400 grams which have an average daily feed intake of 15 g was used. These rats have a comparable body weight to those used by Tullar. This results in a value of approximately 1125 mg/kg/day. This results in a lower predicted NOAEL.

Remark : Average body weights without standard deviation were recorded for each group at approximately weekly intervals. There was no statistical analysis of the data.

Result : There were no serious effects on the acceptability of the feed and had only minor effects on the weight development in the rats. At the end of the study, 3, 2, 7 and 2 of 20 rats died from the control, 0.5, 1.0 and 3.0% groups, respectively. No characteristic gross pathology was evident from the autopsies performed on the respective experimental groups.

Body Weights of rats fed DSTDP
Percent DSTDP in diet

Test day	Control	0.5	1.0	3.0
0	107	97	102	106
90	287	278	277	284
181	326	317	304	309
273	368	373	340	361
371	396	400	372	387
456	397	390	373	383
542	399	394	375	384
630	394	397	374	381
729	374	382	368	377

Source : A.J.Lehman, O.G.Fitzhugh, A.A.Nelson, and G.Woodard , Adv.Food Res.,3,197(1951).

Tullar, P.E. (1947). The pharmacology and toxicology of thiodipropionic acid and its dilauryl and distearyl esters. Final Report. The Kalusowski Memorial Research Laboratories, School of Pharmacy, The George Washington University,

Washington, D.C. Unpublished data. FDA FOIA request #F88-8055. Document #001974-002031.

Reliability : This study is assigned a reliability code of 2e according to the criteria established by Klimisch *et al.* (1997). It was not conducted under GLP or OECD guidelines but generally meets scientific standards, is well documented and is accepted for assessment.

5.5 GENETIC TOXICITY 'IN VITRO'

Type : **Chromosome Aberration Cytogenetic Assay**
System of testing : Chinese Hamster V79 Cells
Concentration : 0, 0.6, 0.75, 1.5, 3.0, 5.0 , 6.0 , 10.0 , 20.0 , 30.0 , 40.0 and 300.0 microg/ml
Cytotoxic conc. : In the absence of S9 mix reduced cell numbers to 55% of control were observed after treatment with 300 ug/ml whereas in the presence of S9 mix no toxic effects were observed.
Metabolic activation : with and without
Result : **negative**
OECD Guide-line 473 "Genetic Toxicology: In Vitro Mammalian Cytogenetic Test"

The test article, formulated in culture medium (MEM) was assessed for its potential to induce structural chromosome aberrations in V79 cells of the Chinese hamster in vitro in two independent experiments. The chromosomes were prepared 18 h ad 28 h after start of treatment with the test article. The treatment interval was 4 h (exp. I: without and with metabolic activation; exp II: with metabolic activation) or 18 h and 28 h without metabolic activation (exp.II). In each experimental group two parallel cultures were set up. Per culture, 100 metaphase plates were scored for chromosome aberrations.

The S9 liver microsomal fraction was obtained from the livers of male Wistar Hanlbm (BRL, CH-4414) and was prepared by the testing facility CCR (an RCC group in Switzerland).

The highest applied concentration in the pre-test was chosen with regard to the properties of the formulation of the test article. A homogenous suspension could be prepared at 300 ug/ml in the absence of S9 mix and 285 ug/ml in the presence of S9 mix. Test article concentrations between 1 and 300 ug/ml (-S9) or 1 and 285 ug/ml (+S9) were chosen for the assessment of the cytotoxic potential.

In the absence of S9 mix reduced cell numbers to 55% of control were observed after treatment with 300 ug/ml whereas in the presence of S9 mix no toxic effects were observed. In the pre-test precipitation of the test article was observed 4 h after start of treatment at concentrations of 5 ug/ml and above in the absence of S9 mix and 10 ug/ml and above in the presence of S9 mix.

In experiment I, test article concentrations within a range of 0.75 – 300 ug/ml (-S9 mix) and 0.6 – 20 ug/ml (+S9 mix) were applied for the investigation of the potential to induce cytogenetic damage. In experiment II, the applied test article concentration ranges were 0.75 – 300 ug/ml (-S9 mix) and 1.0 – 40 ug/ml (+S9 mix).

In the absence and the presence of S9 mix, in both experiments, no reduction of the mitotic index or the cell number was observed, except in the presence of S9 mix in experiment II at interval 28 h after treatment with 40 ug/ml reduced cell numbers were observed.

: In both independent experiments, neither a significant no a biologically relevant increase in the number of cells carrying structural chromosomal aberrations was observed after treatment with the test article.

In addition, no increase in the frequencies of polyploid metaphases was found after treatment with the test article as compared to the frequencies of the controls.

Appropriate mutagens (Ethylmethane sulfonate and Cyclophosphamide) were used as positive controls. They induced statistically significant increase in cells with structural chromosome aberrations.

In conclusion, under the conditions of this study, the test article did not induce structural chromosome aberrations and is considered to be non-mutagenic.

Year : 1998
GLP : yes
Test substance : 95.6% purity; Volatiles <0.1%
Source : In Vitro Chromosome Aberration Assay in Chinese Hamster V79 Cells with TK10594 (IRGANOX PS802). January 5, 1998
Reliability : This study is assigned a reliability code of 1a according to the criteria established by Klimisch *et al.* (1997). It was conducted under GLP and OECD guidelines, is well documented and is acceptable for assessment.

5. Toxicity

Id 693-36-7
Date 02/03/03

Type	:	**Salmonella typhimurium reverse mutation assay**
System of testing	:	Histidine-auxotrophic mutants of S. typhimurium, Strains TA98, TA100, and TA1537
Concentration	:	313 , 625 , 1250 , 2500 and 5000 microg/0.1 ml
Cytotoxic conc.	:	>5000 ug/0.1 ml
Metabolic activation	:	with and without
Result	:	**negative**
Method	:	The tests were carried out in accordance with the method described by Ames et al. 1973, 1973, and 1975.

A preliminary toxicity test was carried out with strain TA100 without activation with the concentrations ranging from 20 to 5000 ug/0.1 ml. Accordingly, the concentration of 5000 ug/0.1 ml was used as the highest in the mutagenicity test and the tests were performed with the following concentrations of the trial substance without and with microsomal activations: 313, 625, 1250, 2500 and 5000 ug/0.1 ml.

: The test substance was dissolved in acetone. Acetone alone was used for the negative controls. The positive control substances were

- 10 ug Daunorubicin-HCL/0.1 ml phosphate buffer for strain TA 98
- 0.25 ug 4-Nitroquinoline-N-oxide/0.1 ml DMSO for strain TA 100
- 100 ug 9(5)-Aminoacridine hydrochloride monohydrate/0.1 ml DMSO for strain TA 1537.
- The activation mixture is tested with all strains and 5 ug 2-aminoanthracene/0.1 ml DMSO.

In the experiments, three Petri dishes are prepared per strain/per concentration. Each Petri dish contains ~20 ml of agar solution plus salts and glucose, 0.1 ml of test solution and 0.1 ml of bacterial culture in 2.0 ml of soft agar. In those dishes with activation, 0.5 ml activation mixture is added.

The source of the metabolic activation (S9) was from the liver of rats (Tif:RAIF(SPF) induced with Aroclor 1254 (Analabs., Inc., North Haven, CT).

In the experiments performed, none of the tested concentrations led to an increase in the incidence of histidine-prototrophic mutants in comparisons with the controls.

Remark Although NOT clearly stated, the S9 fraction was prepared at the CIBA-GEIGY Ltd. Facility in Basle Switzerland.

Year	:	1989
GLP	:	No data
Test substance	:	Purity not stated in report. The specification for commercial grade Irganox PS 802 indicated >95%.
Source	:	Salmonella Mutagenicity Test with Three Strains with TK 10594 (IRGANOX PS 802). Ciba-Geigy Ltd. Basle, Switzerland. June 23, 1989.
Reliability	:	This study is assigned a reliability code of 2e according to the criteria established by Klimisch *et al.* (1997). It was not conducted under GLP or OECD guidelines but generally meets scientific standards, is well documented and is accepted for assessment.

5.6 GENETIC TOXICITY 'IN VIVO'

No data

5.7 CARCINOGENITY

Species	:	rat
Sex	:	male
Strain	:	
Route of admin.	:	Oral feed
Exposure period	:	2 years
Frequency of treatment	:	daily
Post. obs. period	:	
Doses	:	0.5, 1.0 and 3.0%
Result	:	**NOAEL = 3.0% dietary exposure**
Control group	:	yes
Method	:	
Year	:	1944
GLP	:	no
Test substance	:	
Method	:	Two year feeding studies were started in June 1944 at which time groups of 20 rats were placed on diets containing 0.5, 1.0 or 3.0% distearyl thiodipropionate.
Result	:	At the end of 2 years, the results are as follows: (number dead out of 20) - Control group 3/20, 0.5%: 2/20, 1.0%: 6/20 and 3.0%: 2/20. There were no pathological changes noted in the rats fed 3.0% in the diet.
Source	:	A.J.Lehman, O.G.Fitzhugh, A.A.Nelson, and G.Woodard, Adv.Food Res.,3,197(1951).
		Tullar, P.E. (1947). The pharmacology and toxicology of

thiodipropionic acid and its dilauryl and distearyl esters. Final Report. The Kalusowski Memorial Research Laboratories, School of Pharmacy, The George Washington University, Washington, D.C. Unpublished data. FDA FOIA request #F88-8055. Document #001974-002031.

Reliability : This study is assigned a reliability code of 3a according to the criteria established by Klimisch *et al.* (1997). Documentation is insufficient.

5.8 TOXICITY TO REPRODUCTION

Based on the results of the 90-day repeat dose study in **DLTDP (CAS#123-28-4)** it is estimated that this material would not be a reproductive toxicant.

Species	:	rat
Sex	:	10 per sex per group (weeks 1-13); 5 per sex for the control and high dose treatment-free extension groups
Strain	:	Sprague-Dawley; 6 weeks of age at initiation of study.
Route of admin.	:	oral gavage
Body Weight Range	:	Males: 162-193 g; Females: 142-180g (at study initiation)
Exposure period	:	13 weeks with a 4 week treatment-free period.
Frequency of treatment	:	daily
Post obs. period	:	yes, 4 weeks
Doses	:	125, 350, and 1000 mg/kg/day
Control group	:	yes
Method	:	13 Week Oral (gavage) Toxicity Study in the Rat followed by a 4 Week Treatment-free Period.
Summary Result	:	**NOAEL = 350 mg/kg/day; NOEL = 125 mg/kg/day**
Year	:	1993
GLP	:	Yes
Test substance	:	**DLTDP (CAS#123-28-4)**
Method	:	Groups of 10 rats per sex per group were given doses of 0, 125, 350, or 1000 mg/kg/day by gavage, using a metal cannula for approximately 13 weeks. Dosing solutions were made daily and concentrations were analytically confirmed at weeks 1, 4, 8, and 13. Animals were housed in groups of 5 of the same sex and dose group per cage. The animal room was maintained at 19-25C, 35-75% relative humidity, and a 12 hour light/12 hour dark lighting cycle. Rats were fed ad lib, but fasted ~16 hours prior to blood sampling, during the collection of urine, and before necropsy. Water was also provided ad lib, but withheld during urine collection. All animals were observed twice daily for morbidity and mortality. Clinical observations were done daily, with full clinical evaluations done weekly. Body weights and food consumption were

recorded weekly. Opthalmoscopy was performed on all animals pretest and at week 13 in the control and high dose animals. Clinical pathology was performed on 10 animals/sex in control and high dose groups after week 4, 10 animals/sex in all groups after week 13, and in all recovery animals after week 17. Parameters included hematology (except on treatment-free period animals), blood clinical chemistry, and urinalysis. All animals were submitted to full necropsy. Organ weights were taken at necropsy. Histopathology was performed on all selected organs/tissues for all animals in the control and high dose groups, the liver, kidneys and lungs for all animals in all groups, and the heart from animals in groups 2 and 3 and in all recovery group animals. The hearts from all animals was examined after PTAH staining.

Remark : **Organs examined histologically also included the epidiymides, mammary glands, ovaries, prostate, seminal vesicles, testes, uterus (horn + cervix). This is suggestive of no adverse effects on reproduction.**

Result : There were no unscheduled deaths and no treatment related clinical signs. There were no treatment related differences in body weight gain and food consumption was unaffected by treatment. There were no treatment related eye lesions. None of the hematological parameters were considered to represent an adverse effect of treatment. None of the clinical chemistry parameters other than a reversible elevation in serum cholesterol in the high dose females and a reversible elevation of alanine and aspartate aminotransferase activities in all high dose animals were related to an effect of treatment. Urine parameters were unaffected other than being slightly more acidic in the high dose animals as compared to the controls. This was reversible after the 4 week treatment-free period. The minor differences in the weight of the major organs were considered of no toxicological significance in the absence of microscopic lesions. Macroscopic changes were considered to either be agonal or incidental in origin or unrelated to treatment. The treatment related microscopic lesions were seen in the heart of high dose animals. The lesion was described as small foci of degenerated or necrotic fibers associated with minimal to moderate mononuclear cell infiltration. This association suggested early or ongoing myocarditis. These lesions were not present in animals previously treated at the high dose level but allowed a 4 week period without treatment. There were no other treatment related microscopic lesions.

In conclusion, the oral (gavage) administration of DLTDP to the rat for 13 weeks at a dose level of 1000 mg/kg/day was associated with a minor increase in serum cholesterol

concentrations in females, increased serum ALAT and ASAT activities and decreased urinary pH in both sexes. Microscopic findings in the heart of these animals suggested on ongoing myocarditis. The heart was therefore identified as the target organ. All these changes were reversible after 4 weeks without treatment. At a dose level of 350 mg/kg/day there was no evidence for any microscopic change in the heart and not other differences to indicate an adverse effect of the test article. This dose level is therefore considered to be the no observed adverse effect level for DLTDP in the rat. There were no changes considered to represent an effect of the test article at 125 mg/kg/day and therefore this dose level is considered to be the no observed effect level for DLTDP in the rat.

Source : 13 Week Oral (gavage) Toxicity Study in the Rat followed by a 4 Week Treatment-free Period. Ciba-Geigy Ltd. Basel Switzerland. December 14, 1993.

Reliability : This study is assigned a reliability code of 1b according to the criteria established by Klimisch *et al.* (1997). It was conducted under GLP guidelines but uses a non-specified protocol method that generally meets scientific standards, is well documented and is acceptable for assessment.

5.9 DEVELOPMENTAL TOXICITY/TERATOGENICITY

Based on the results of teratogenicity assays in four species using **DLTDP (CAS#123-28-4)** it is estimated that this material would not be a teratogen.

Species	:	**rat**
Sex	:	female
Strain	:	Wistar
Route of admin.	:	gavage
Exposure period	:	
Frequency of treatment	:	
Duration of test	:	
Doses	:	16, 74, 350 or 1600 mg/kg
Control group	:	yes
NOAEL Maternalt.	:	**= 1600 mg/kg bw**
NOAEL Teratogen	:	**= 1600 mg/kg bw**
Method	:	other: essentially follows OECD 414
Year	:	1972
GLP	:	no
Test substance	:	**DLTDP (CAS#123-28-4)**
Method	:	A positive control group received 250 mg/kg aspirin. Frequency of treatment for positive control group not stated. The number of pregnant rats at the end of the study ranged

		from 19-21/dose level. Feed and water were available ad libitum. The rats were observed daily for general appearance and behavior, with emphasis on feed consumption and weight. Weights were obtained on days 0, 6, 11, 15 and 20 of gestation. On day 20 of gestation caesarian sections were performed and the numbers of implantation and resorption sites as well as the numbers of live and dead fetuses were recorded. The urogenital tract of each dam was examined for any abnormality, all fetuses were examined for any gross external abnormalities, and all live pups were weighed. Visceral examinations were performed on one-third of the fetuses of each litter, and the remaining two-thirds were examined for skeletal defects.
Result	:	No adverse effects with respect to number of implantations and maternal or fetal death were noted after oral administration to rats of up to 1600 mg/kg dilauryl thiodipropionic acid on days 6-15 of gestation. There were no significant differences in numbers of abnormalities of the soft or skeletal tissues between the treated and sham control fetuses.
Flag	:	Critical study for SIDS endpoint
Source	:	Food and Drug Research Labs, Inc. (FDRL). (Dec. 29, 1972). Teratologic evaluation of FDA 71-40 (Dilauryl thiodipropionic acid) in mice, rats, and hamsters. Springfield, VA: U.S. Department of Commerce, National Technical Information Service (NTIS). NTIS publication #PB221 77.
Reliability	:	This study is assigned a reliability code of 1b according to the criteria established by Klimisch *et al.* (1997). It was not conducted under GLP guidelines but uses methods that generally meet scientific standards, is well documented and is acceptable for assessment.
Species	:	**mouse**
Sex	:	female
Strain	:	CD-1
Route of admin.	:	gavage
Exposure period	:	days 6-15
Frequency of treatment	:	daily
Duration of test	:	
Doses	:	16, 74, 350 and 1600 mg/kg
Control group	:	yes
NOAEL Maternalt.	:	**= 1600 mg/kg bw**
NOAEL Teratogen	:	**= 1600 mg/kg bw**
Method	:	other: essentially follows OECD 414
Year	:	1972
GLP	:	no
Test substance	:	**DLTDP (CAS#123-28-4)**

Method	:	A positive control group received 150 mg/kg aspirin. Frequency of treatment for the positive control not stated. The number of pregnant mice at the end of the study ranged from 20-22/dose level. Feed and water were available ad libitum. The mice were observed daily for general appearance and behavior, with emphasis on feed consumption and weight. Weights were obtained on days 0, 6, 11, 15 and 17 of gestation. On day 17 of gestation caesarian sections were performed and the numbers of implantation and resorption sites as well as the numbers of live and dead fetuses were recorded. The urogenital tract of each dam was examined for any abnormality, all fetuses were examined for any gross external abnormalities, and all live pups were weighed. Visceral examinations were performed on one-third of the fetuses of each litter, and the remaining two-thirds were examined for skeletal defects.
Result	:	No adverse effects were found with respect to implantations and maternal and fetal survival after oral administration to mice of up to 1600 mg/kg TDPA on days 6-15 of gestation. The number of abnormalities seen in the soft or skeletal tissues of the treated fetuses was comparable to that seen in the sham control fetuses.
Source	:	Food and Drug Research Labs, Inc. (FDRL). (Dec. 29, 1972). Teratologic evaluation of FDA 71-40 (Dilauryl thiodipropionic acid) in mice, rats, and hamsters. Springfield, VA: U.S. Department of Commerce, National Technical Information Service (NTIS). NTIS publication #PB221 77.
Reliability	:	This study is assigned a reliability code of 1b according to the criteria established by Klimisch *et al.* (1997). It was not conducted under GLP guidelines but uses methods that generally meet scientific standards, is well documented and is acceptable for assessment.

Species	:	**rabbit**
Sex	:	female
Strain	:	Dutch
Route of admin.	:	gavage
Exposure period	:	days 6-18 of gestation
Frequency of treatment	:	daily
Duration of test	:	
Doses	:	2.5, 10, 45, 216, 1000 mg/kg
Control group	:	yes
NOAEL Maternalt.	:	**= 1000 mg/kg bw**
NOAEL Teratogen	:	**= 1000 mg/kg bw**
Method	:	other: essentially follows OECD 414
Year	:	1973
GLP	:	no

Test substance	:	**DLTDP (CAS#123-28-4)**
Method	:	Groups of 15-29 artificially inseminated females/dose level resulted in 8-13 pregnant rabbits/dose level. On day 29, all does were subjected to c-section. The numbers of corpora lutea, implantation sites, resorption sites, and live and dead fetuses recorded. The body weights of the live pups were also recorded. The urogenital tract of each animal was examined in detail for normality. All fetuses underwent a detailed gross examination for the presence of external congenital abnormalities. The live fetuses of each litter were then placed in an incubator for 24 hours for the evaluation of neonatal survival. All surviving pups were sacrificed, and all pups examined for visceral abnormalities by dissection. All fetuses were then cleared in potassium hydroxide, stained with alizarin red S dye and examined for skeletal defects.
Result	:	Eight to thirteen pregnant dams survived to term. There was no clearly discernible effect on nidation or on maternal or fetal survival at doses as high as 1000 mg/kg. The number of abnormalities seen in either soft or skeletal tissues of the test groups did not differ from the number occurring spontaneously in the control
Flag	:	Critical study for SIDS endpoint
Source	:	FDA (1973). Teratologic evaluation of FDA 71-40 (dilauryl thiodipropionic acid) NTIS PB-223 824.
Reliability	:	This study is assigned a reliability code of 1b according to the criteria established by Klimisch *et al.* (1997). It was not conducted under GLP guidelines but uses methods that generally meet scientific standards, is well documented and is acceptable for assessment.
Species	:	**hamster**
Sex	:	female
Strain	:	other: golden
Route of admin.	:	gavage
Exposure period	:	Day 6-10 of gestation
Frequency of treatment	:	daily
Duration of test	:	
Doses	:	16, 74, 350 or 1600 mg/kg
Control group	:	yes
NOAEL Maternalt.	:	**= 1600 mg/kg bw**
NOAEL Teratogen	:	**= 1600 mg/kg bw**
Method	:	other: essentially follows guideline 414
Year	:	1972
GLP	:	no
Test substance	:	**DLTDP (CAS#123-28-4)**
Method	:	The number of hamsters at the end of the study ranged from 20-23/dose level. Feed and water were available ad libitum.

The hamsters were observed daily for general appearance and behavior, with emphasis on feed consumption and weight. Weights were obtained on days 0, 8, 10 and 14 of gestation. On day 14 of gestation caesarian sections were performed and the numbers of implantation and resorption sites as well as the numbers of live and dead fetuses were recorded. The urogenital tract of each dam was examined for any abnormality, all fetuses were examined for any gross external abnormalities, and all live pups were weighed. Visceral examinations were performed on one-third of the fetuses of each litter, and the remaining two-thirds were examined for skeletal defects.

Result : The numbers of implantations and maternal and fetal survival were not adversely affected by oral administration to hamsters of up to 1600 mg/kg TDPA on days 6-10 of gestation. No significant differences in the number of soft or skeletal tissue abnormalities were found between treated and sham control fetuses.

Source : Food and Drug Research Labs, Inc. (FDRL). (Dec. 29, 1972). Teratologic evaluation of FDA 71-40 (Dilauryl thiodipropionic acid) in mice, rats, and hamsters. Springfield, VA: U.S. Department of Commerce, National Technical Information Service (NTIS). NTIS publication #PB221 77.

Reliability : This study is assigned a reliability code of 1b according to the criteria established by Klimisch *et al.* (1997). It was not conducted under GLP guidelines but uses methods that generally meet scientific standards, is well documented and is acceptable for assessment.

5.10 OTHER RELEVANT INFORMATION

Type : Excretion

Method : Groups of 6 rats fed diets containing 3.0% distearyl thiodipropionate were placed in individual metabolism cages for 48 hours. Feces and urine were collected over the 48 hour period and examined for thiodipropionates.

Source : Tullar, P.E. (1947). The pharmacology and toxicology of thiodipropionic acid and its dilauryl and distearyl esters. Final Report. The Kalusowski Memorial Research Laboratories, School of Pharmacy, The George Washington University, Washington, D.C. Unpublished data. FDA FOIA request #F88-8055. Document #001974-002031.

A.J.Lehman, O.G.Fitzhugh, A.A.Nelson, and G.Woodard, Adv.Food Res.,3,197(1951)

AFREAW Advances in Food Research (1951). Academic Press Inc., 1 E. First St., Duluth MN 55802. Vol 3:197.

Ames et al., An improved Bacterial Test System for the Detection and Classification of Mutagens and Carcinogens. Proc.Natl.Acad.Sci. USA 70, 782-786

Ames et al., Carcinogens and Mutagens: A Simple Test Method Combining Liver Homogenates for Activationand Bacteria for Detection. Proc.Natl.Acad.Sci. USA 70, 2281-2285

Ames et al., Methods for Detecting Carcinogens and Mutagens with the salmonella/Mammalian-Microsome Mutagenicity Test. Mutation Res. 31, 347-364

Blok, J., de Morsier, AA., Gerike, P., Reynolds, L. and Wellens, H. (1985). Harmonisation of ready biodegradability tests. Chemosphere 14:1805-1820.

Ciba Additive GmbH Lampertheim
Ciba Specialty Chemicals Inc. Basel
Ciba Spezialitaetenchemie Lampertheim GmbH formerly CIBA Additive GmbH Lampertheim
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)

Clariant GmbH (1994), EG-Sicherheitsdatenblatt (29.08.94)

CYTEC MSDS (9/01/98). CYANOX STDP Antioxidant MSDS.

FDA (1973). Teratologic evaluation of FDA 71-40 (dilauryl thiodipropionic acid) NTIS PB-223 824.

Food and Drug Research Labs, Inc. (FDRL). (Dec. 29, 1972). Teratologic evaluation of FDA 71-40 (Dilauryl thiodipropionic acid) in mice, rats, and hamsters. Springfield, VA: U.S. Department of Commerce, National Technical Information Service (NTIS). NTIS publication #PB221 77.

Hampshire MSDS (2000).

Hoechst AG (1995): EG-Sicherheitsdatenblatt Hostanox SE 4 (19.05.1995)

In Vitro Chromosome Aberration Assay in Chinese Hamster V79 Cells with TK10594 (IRGANOX PS802). January 5, 1998

Keeler, P.A. and Olson, K.J. (1975). Toxicological properties and industrial handling hazards of distearyl thiodipropionate. Unpublished report of The Dow Chemical Company.

Klimisch, H.J., Andreae, M and Tillman, U. A systemic approach for evaluating the quality of experimental toxicological and ecotoxicological data. *Regulatory Toxicology and Pharmacology*. 25: 1-5, 1997.

Report on the 13 Week Oral (gavage) Toxicity Study in the Rat followed by a 4 Week Treatment-free Period. Ciba-Geigy Ltd. Basel Switzerland. December 14, 1993.

Report on the Growth Inhibition Test of IRGANOX PS 802 to Green Algae (Scenedesmus subspicatus), Ciba-Geigy Ltd. Basle, Switzerland. December 17, 1992.

Report on the Test for Acute Toxicity of IRGANOX PS 802 to Zebra-Fish, Ciba-Geigy Ltd. Basle, Switzerland. January 9, 1989.

Report on the Test for Acute Toxicity of TK10594 to Daphnia Magna, Ciba-Geigy Ltd. Basle, Switzerland. December 16, 1988.

Report on the Test for Ready Biodegradability of TK10594 in the Modified Sturm Test, Ciba-Geigy Ltd. Basle, Switzerland. April 4, 1989.

Salmonella Mutagenicity Test with Three Strains with TK 10594 (IRGANOX PS 802). Ciba-Geigy Ltd. Basle, Switzerland. June 23, 1989.

Syracuse Research Corporation, Syracuse, NY and U.S. Environmental Protection Agency, Office of Pollution Prevention and Toxics (2000).

Tullar, P.E. (1947). The pharmacology and toxicology of thiodipropionic acid and its dilauryl and distearyl esters. Final Report. The Kalusowski Memorial Research Laboratories, School of Pharmacy, The George Washington University, Washington, D.C. Unpublished data. FDA FOIA request #F88-8055. Document #001974-002031.

7. Klimisch Evaluation

Id 693-36-7
Date 02/03/03

Klimisch, H.J., Andreae, M and Tillman, U. A systemic approach for evaluating the quality of experimental toxicological and ecotoxicological data. *Regulatory Toxicology and Pharmacology*. 25: 1-5, 1997.

1 = Valid without restriction

1a: GLP guideline study
1b: Comparable to guideline study
1c: Meets national standard methods (AFNOR/DIN)
1d: Meets generally accepted scientific standards and is described in sufficient detail

2 = Valid with restriction

2a: Guideline study without detailed documentation
2b: Guideline study with acceptable restrictions
2c: Comparable to guideline study with acceptable restrictions
2d: Meets national standard methods with acceptable restrictions
2e: Meets generally accepted scientific standards, well-documented and acceptable for assessment
2f: Accepted calculation method
2g: Data from Handbook or collection of data

3 = Invalid

3a: Documentation insufficient for assessment
3b: Significant methodological deficiencies
3c: Unsuitable test system

4 = Insufficient Documentation

4a: Abstract
4b: Secondary literature
4c: Original reference not yet available
4d: Original reference in foreign language
4e: Documentation insufficient for assessment

3,3'-thiodipropionic acid, ditridecyl ester

Id 10595-72-9
Date 02/03/03

I U C L I D

Data Set

Existing Chemical : ID: 10595-72-9
CAS No. : 10595-72-9

COMPANY INFORMATION

Name of Producer	:	Hampshire Chemical Corp., a wholly owned subsidiary of The Dow Chemical Company.
Street	:	45 Hayden Ave. Suite 2500
Town	:	Lexington, MA 02421-7994
Country	:	United States
Name of Producer	:	Cytec Industries Inc.
Street	:	5 Garret Mountain Plaza
Town	:	West Paterson, NJ 07424
Country	:	United States

1.1 GENERAL SUBSTANCE INFORMATION

Substance type	:	organic
Physical status	:	liquid
Purity	:	ca. 99 % w/w
Source	:	Hampshire MSDS (09-14-99). Ditridecyl thiodipropionate MSDS.

1.2 SYNONYMS

Propanoic acid, 3,3'-thiobis-, ditridecyl ester
3,3'-Thiodipropionate de di(tridecyle) (French)
di(tridecyl) 3,3'-thiodipropionate
Di(tridecyl)-3,3'-thiodipropionat (German)
3,3'-tiodipropionato de di(tridecilo) (Spanish)
Propanoic acid, 3,3'-thiobis-, ditridecyl ester
3,3'-Thiobis propanoic acid ditridecyl ester

OTHER NAME(S):
ADK Stab AO 503
ADK Stab AO 503A
Bis(tridecyl) 3,3'-thiodipropionate
Bis(tridecyl) thiodipropionate
Cyanox 711
Ditridecyl 3,3'-thiodipropionate
Ditridecyl thiodipropionate
Evanstab 13
Mark AO 503
Mark AO 503A
Plastanox 711
Propionic acid, 3,3'-thiodi-, ditridecyl ester

1.3 IMPURITIES

CAS-No	:	112-70-9
EINECS-No	:	203-998-8
EINECS-Name	:	tridecan-1-ol
Contents	:	ca. 1 % w/w
Source	:	Hampshire MSDS (09-14-99). Ditridecyl thiodipropionate MSDS.

2.1 MELTING POINT

Value	:	**< 25 ° C**
Sources	:	Dow Chemical Co. (09/14/99). Ditridecyl thiodipropionate. Dow Chemical Co. MSDS.
Reliability	:	The values from a collection of data are assigned a reliability code of 2g according to the criteria established by Klimisch *et al.* (1997).

2.2 BOILING POINT

Test substance	:	as prescribed by 1.1 - 1.4
Remark	:	Not applicable. Material decomposes at 226C. Boiling point is >226C.

2.3 DENSITY

Type	:	relative density
Value	:	= 0.936 at ° C
Method	:	
Year	:	
GLP	:	
Test substance	:	as prescribed by 1.1 - 1.4
Sources	:	Hampshire MSDS (9-14-99). Ditridecyl thiodipropionate MSDS. CYTEC MSDS (5/21/99). CYANOX 711 Antioxidant MSDS.
Reliability	:	The values from a collection of data are assigned a reliability code of 2g according to the criteria established by Klimisch *et al.* (1997).

2.4 VAPOUR PRESSURE

Value	:	**= 2.27e-09 at 25° C**
Decomposition	:	
Method		other (calculated): MPBPWIN version 1.40
Year	:	2001
GLP	:	Not applicable to estimations
Test substance	:	as prescribed by 1.1 - 1.4
Source	:	Estimated by the MPBPWIN Program (v.1.40), using Modified Grain Method. Syracuse Research Corporation, Syracuse, NY and U.S. Environmental Protection Agency, Office of Pollution Prevention and Toxics (2000).

Reliability	:	The vapor pressure determination from an accepted calculation method is assigned a reliability code of 2f according to the criteria established by Klimisch *et al.* (1997).

2.5 PARTITION COEFFICIENT

Log pow	:	**= 12.77 at 25° C**
Method		other (calculated): KOWWIN version 1.66
Year	:	2001
GLP	:	Not applicable to estimations
Test substance	:	as prescribed by 1.1 - 1.4
Source	:	Estimated by the KowWin Program (v.1.66) Syracuse Research Corporation, Syracuse, NY and U.S. Environmental Protection Agency, Office of Pollution Prevention and Toxics (2000).
Reliability	:	The partition coefficient determination from an accepted calculation method is assigned a reliability code of 2f according to the criteria established by Klimisch *et al.* (1997).

2.6 WATER SOLUBILITY

Value	:	**4.717e-9 mg/l at 25 ° C**
Qualitative	:	
Pka	:	at 25 ° C
PH	:	at and ° C
Method	:	other: (calculated) WSKOW version 1.40
Year	:	2001
GLP	:	Not applicable to estimations
Test substance	:	as prescribed by 1.1 - 1.4
Source	:	Estimated from Kow with WSKOW (v1.40) : KowWin Estimate Syracuse Research Corporation, Syracuse, NY and U.S. Environmental Protection Agency, Office of Pollution Prevention and Toxics (2000).
Reliability	:	The water solubility determination from an accepted calculation method is assigned a reliability code of 2f according to the criteria established by Klimisch *et al.* (1997).
Remark	:	Considered insoluble in water.
Source	:	Cytec (05/21/1999) Cyanox 711 antioxidant. Cytec MSDS
Remark	:	Solubility in water is negligible.
Source	:	Hampshire MSDS (9-14-99). Ditridecyl thiodipropionate MSDS.

Reliability	:	The values from a collection of data are assigned a reliability code of 2g according to the criteria established by Klimisch *et al.* (1997).

2.7 FLASH POINT

Value	:	> 110 ° C
Type	:	closed cup
Method	:	
Year	:	
GLP	:	
Test substance	:	as prescribed by 1.1 - 1.4
Source	:	Cytec (05/21/1999) Cyanox 711 antioxidant. Cytec MSDS.
Value	:	= 152 ° C
Type	:	open cup
Method	:	
Year	:	
GLP	:	
Test substance	:	as prescribed by 1.1 - 1.4
Source	:	Hampshire MSDS (9-14-99). Ditridecyl thiodipropionate MSDS.
Reliability	:	The values from a collection of data are assigned a reliability code of 2g according to the criteria established by Klimisch *et al.* (1997).

3.1 PHOTODEGRADATION

Type	:	air
Light source	:	
Light spect.	:	nm
Rel. intensity	:	based on Intensity of Sunlight
Direct photolysis		
Half-life t1/2	:	**= 2.338 hour(s)**
		For reaction with hydroxyl radicals, the predicted half-life of the chemical is relatively rapid
Degradation	:	% after
Quantum yield	:	
Indirect photolysis		
Sensitizer	:	
Conc. of sens.	:	
Rate constant	:	**= 54.9032 E-12 cm3/(molecule*sec)**
Degradation	:	% after
Deg. Product	:	
Method	:	other (calculated): AOP version 1.90
Year	:	2001
GLP	:	Not applicable to estimations
Test substance	:	as prescribed by 1.1 - 1.4
Reference	:	Estimated by the AOP program (v1.90), which estimates rate constants and half-lives of atmospheric reactions of organic compounds with hydroxyl radicals and ozone in the atmosphere. Syracuse Research Corporation, Syracuse, NY and U.S. Environmental Protection Agency, Office of Pollution Prevention and Toxics (2000).
Reliability	:	The values determined by an accepted calculation method are assigned a reliability code of 2f according to the criteria established by Klimisch *et al.* (1997).

3.2 STABILITY IN WATER

Not Applicable: Due to Insolubility of Material.

3.3 TRANSPORT BETWEEN ENVIRONMENTAL COMPARTMENTS

MacKay Level III Fugacity Model

Medium	Concentration %	Emissions (kg/hr)
Air	**0.271**	**1000**
Water	**7.03**	**1000**
Soil	**30.3**	**1000**
Sediment	**62.4**	**0**
Persistence Time		**653 hr**

Medium	Concentration %	Emissions (kg/hr)
Air	**5.26**	**1000**
Water	**2.14**	**0**
Soil	**73.6**	**0**
Sediment	**19**	**0**
Persistence Time		**101 hr**

Medium	Concentration %	Emissions (kg/hr)
Air	**1.6e-10**	**0**
Water	**10.1**	**1000**
Soil	**2.23e-09**	**0**
Sediment	**89.9**	**0**
Persistence Time		**1.34e+3 hr**

Medium	Concentration %	Emissions (kg/hr)
Air	**5e-13**	**0**
Water	**1.36e-3**	**0**
Soil	**100**	**1000**
Sediment	**1.2e-2**	**0**
Persistence Time		**520 hr**

Reference Estimated by the Level III Fugacity Model (Full-Output)

Syracuse Research Corporation, Syracuse, NY and U.S. Environmental Protection Agency, Office of Pollution Prevention and Toxics (2000).

Reliability : The values determined by an accepted calculation method are assigned a reliability code of 2f according to the criteria established by Klimisch *et al.* (1997).

3.4 BIODEGRADATION

No data. Estimated to be **Not Readily Biodegradable** based on data for DLTDP (CAS# 123-28-4) and DSTDP (CAS#693-36-7), however, DLTDP and DSTDP are considered to be **inherently biodegradable** based on data for DSTDP in the OECD 302C Test for Inherent Biodegradability.

Type : Aerobic
Inoculum : Bacteria collected from activated sludge of the sewage treatment plant of CH – 4153 Reinach on 2/1/89.
Contact time : 28 days
Degradation : = 25 % after 28 day (10.9 mg test substance/L)
= 57 % after 28 day (19.9 mg test substance/L)
Result : **Not Readily Biodegradable**

Method : OECD Guide-line 301 B "Ready Biodegradability: Modified Sturm Test (CO2 evolution)"

- 2-liter flasks equipped with gas inlet and magnetic stirrers were used as the test vessels. The test medium was prepared according to the method described in the guideline. The temperature was maintained at 22 ± 2 °C, 28 days. Aeration consisted of ~ 25 ml/min air free of carbon dioxide.
- Reference Substance: 20 mg/L with 0.5 ml of the nonylphenol 10EO5PO.
- Test Substance: 10.9 mg/L and 19.9 mg/L
- 1200 ml of the mineral solution with the inoculum was aerated for 24 hours in the test vessel. In 300 ml mineral solution 0.5 ml nonylphenol 10EO5PO (solution of 30 mg in 100 ml bidist. Water) and 16.3 rsp. 29.9 mg of test substance were added and homogenized. This solution was given to the test vessel which was immediately connected to the CO2 traps.
- Blank: Water as specified in the guideline containing 0.5 ml of the nonylphenol 10EO5PO solution.
- Measurements: Determination of the initial CO2 of the 0.05 N sodium hydroxide and the CO2, absorbed in the absorbers filled with 200 ml 0.05 N sodium hydroxide on the days 6, 10, 13, 17, 20 (only for blank and reference), 21, 24, 27, and 28.
- The biodegradation was calculated on the basis of the theoretical carbon content of the test substance and the cumulative quantities of carbon dioxide determined on the days of measurements. For the calculation the formula given in the guideline was used.
- Reference Substance Biodegradation: 20 mg/L = 84.3% in 28 days.
- Test Substance: 10.87 mg/L = 25% in 28 days & 19.93 mg/L = 57% in 28 days.

Year : 1989
GLP : In spirit of GLP
Test substance : **DLTDP (CAS# 123-28-4)**
Remark : Due to the poor solubility of the test material in water, an emulsifier was used to achieve a better distribution in the

medium. The test substance was added to the medium, homogenized with nonylphenol 10EO5PO.

The volume of the test solution was reduced from 3L to 1.5L. The CO2 formed by biodegradation was absorbed with NaOH and determined on a carbon analyzer.

Source	:	Report on the Test for Ready Biodegradability of TK10030 in the Modified Sturm Test, Ciba-Geigy Ltd. Basle, Switzerland. February 21, 1989.
Reliability		This study is assigned a reliability code of 1b according to the criteria established by Klimisch et al. (1997). It was conducted under OECD guidelines.
Type	:	aerobic
Inoculum	:	
Contact time	:	
Degradation	:	**= 60 %**
Result	:	**Inherently Biodegradable**
Deg. Product	:	NA
Method	:	OECD Guide-line 302 C "Inherent Biodegradability: Modified MITI Test (II)"
Year	:	1980
GLP	:	No data
Test substance	:	**DSTDP (CAS#693-36-7)**
Remark	:	Results are the average of testing done at five separate testing facililties in a series of round robin tests to compare the results of various inherently biodegradeability tests.
Source		Blok, J., de Morsier, AA., Gerike, P., Reynolds, L. and Wellens, H. (1985). Harmonisation of ready biodegradability tests. Chemosphere 14:1805-1820.
Reliability		This study is assigned a reliability code of 1d according to the criteria established by Klimisch et al. (1997). It was conducted under OECD guidelines.

4.1 ACUTE/PROLONGED TOXICITY TO FISH

No data. Estimated to be approximately >71 mg/L based on for DLTDP (CAS# 123-28-4).

Type	:	OECD Guideline 203
Species	:	Zebra-Fish (Brachydanio rerio)
Exposure period	:	96 hour(s)
Unit	:	mg/l
Analytical monitoring	:	yes
LC50	:	**>71 mg/L**
Method	:	10 fishes per concentration and control, 10 fish per aquarium. The fish were ~26 mm in length, 0.15 g. The fish were not fed for 24 hours prior to exposure. The Glass aquaria were 20L capacity with 15 L dechlorinated tap water, hardness 176 mg CaCO3/L, temperature 23 ± 1°C. The aquaria were gently aerated during the test; the fish were provided fluorescent lighting 16 hours daily. Oxygen, pH, and temperature were measure daily. Due to the poor solubility of the test material in water, a stock solution of 4 g of the test substance and 40 mg alkylphenol-polyglycolether were mixed and made with 10 ml tetrahydrofuran. This solution was diluted appropriately. The nominal test concentrations were 10, 18, 32, 58, and 100 mg/L. Control = Water plus 132 mg tetrahydofuran and 1 mg alkylphenol-polyglycolether per liter water in the concentration used for the highest test concentration. Initially small parts of the test substance floated at the surface of all test concentrations and a slight deposit was observed after 72 hours of exposure in all test vessels. The analytically confirmed concentrations were 5.2, 11, 19, 46, and 71 mg/L. None of the fish died in any of the test vessels and there were no signs of altered swimming behavior, loss of equilibrium, respiratory effects, exopthalmus or pigmentation changes.
Year	:	1988
GLP	:	In spirit of GLP
Test substance	:	**DLTDP (CAS# 123-28-4)**
Remark	:	96Hr LC50 is equivalent to highest concentration tested; thus value may be higher than reported.
Source	:	Report on the Test for Acute Toxicity of TK10030 to Zebra-Fish, Ciba-Geigy Ltd. Basle, Switzerland. December 2, 1988.
Reliability		This study is assigned a reliability code of 1b according to the

criteria established by Klimisch et al. (1997). It was conducted under OECD guidelines.

4.2 ACUTE TOXICITY TO AQUATIC INVERTEBRATES

No data. Estimated to be approximately 10 mg/L based on for DLTDP (CAS# 123-28-4).

Type	:	OECD Guideline 202
Species	:	Daphnia Magna Straus 1820
Exposure period	:	48 hour(s)
Unit	:	mg/l
Analytical monitoring	:	yes
LC50	:	**10 mg/L**
Method	:	20 daphnia per concentration and control, 4 replicates of 5 daphnia each. The daphnia were not fed during the test. The daphnia were obtained from in-house cultures at Ciba-Geigy Ltd., Basle, Switzerland. The water was reconstituted water prepared in a 1000 ml beaker; total hardness was 240 mg CaCO3/L. The water was aerated with clean air for at least 24 hrs before use. The daphnia were placed in 100 ml solution per beaker, covered with watch glasses. The temperature was maintained at 20 ± 1°C, 16 hours fluorescent lighting daily. Oxygen, pH, and temperature were checked at the start of the test. Due to the poor solubility of the test material in water, a stock solution of 2.5 g of the test substance and 40 mg alkylphenol-polyglycolether were mixed and made with 10 ml tetrahydrofuran. This solution was diluted to 100 mg/l with water. Control = Water plus 82.7 mg tetrahydofuran and 0.5 mg alkylphenol-polyglycolether per liter water in the concentration used for the highest test concentration. Nominal test concentrations were 3.2, 5.8, 10, 18, and 32 mg/L. Test material was added to the water prior to transfer in of the daphnia. A slight deposit was observed at all concentrations. The EC0 was determined to be <3.2 mg/L and the EC100 was determined to be 18 mg/L.
Year	:	1988
GLP	:	In spirit of GLP
Test substance	:	**DLTDP (CAS# 123-28-4)**
Remark	:	None
Source	:	Report on the Test for Acute Toxicity of TK10030 to Daphnia Magna, Ciba-Geigy Ltd. Basle, Switzerland. November 25,

1988.

Reliability This study is assigned a reliability code of 1b according to the criteria established by Klimisch et al. (1997). It was conducted under OECD guidelines.

4.3 TOXICITY TO AQUATIC PLANTS E.G. ALGAE

No data. Estimated to be approximately >33.9 mg/L based on for DLTDP (CAS# 123-28-4).

Species	:	Green Algae (Scenedesmus subspicatus)
Type	:	87/302/EEC Algae Growth Inhibition Test
Endpoint	:	biomass
Exposure period	:	72 hour(s)
Unit	:	mg/l
Analytical monitoring	:	Values based on nominal concentrations
EbC50	:	**33.9 mg/L**
NOEbC (0-72 h)	:	11.0mg/L
Method	:	100 ml Erlenmeyer flasks with 50 ml test solution per flask were used. The temperature was maintained at 24 ± 1°C. Lighting was continuous cold white fluorescent light, 133 uE/m2 sec ± 20 %. Test concentrations were nominal determined to be 1.23, 3.7, 11, 33, and 100 mg/L. 3.0 g test substance and 3.0 g vehicle (96% n,n-dimethylformamide and 4% alkyl-phenol-polyglycolether (ARKOPAL)) were mixed together for 24 hours. 1 g of this blend was mixed with 9 g water and then 2 ml of this blend was mixed and made up to 1000 ml with water, achieving a concentration of 100 mg/L. Water plus vehicle was used as the blank. Each test concentration was tested in 3 replicates, the blank control in 6. Calculated amounts of the stock solution to produce the desired test concentrations were given into the water and were homogeneously distributed. The algae were then transferred into the flasks. The test substance was homogeneously distributed in the test vessels at all test times and test concentrations. Cell densities were measured at 24, 48, and 72 hours exposure on a TOA cell counter. Temperature was continuously measured and maintained at 23 ± 1°C. pH was measured at 0h and 72h exposure. The EbC 50 (0-72 h) = 33.9 mg/L 95% CL 29.5-38.3 mg/L. The NOEbC (0-72 h) (5% level = 11.0 mg/L).
Year	:	1992

GLP	:	In spirit of GLP
Test substance	:	**DLTDP (CAS# 123-28-4)**
Remark	:	Values based on nominal concentrations.
Source	:	Report on the Growth Inhibition Test of IRGANOX PS 800 to Green Algae (Scenedesmus subspicatus), Ciba-Geigy Ltd. Basle, Switzerland. September 16, 1992.
Reliability		This study is assigned a reliability code of 1b according to the criteria established by Klimisch et al. (1997). It was conducted under OECD guidelines.

5.1 ACUTE ORAL TOXICITY

Type	:	LD50
Species	:	rat
Strain	:	
Sex	:	female
Number of animals	:	
Vehicle	:	other: corn oil
Value	:	**> 2000 mg/kg bw**
Method	:	
Year	:	1974
GLP	:	no
Test substance	:	as prescribed by 1.1 - 1.4
Method	:	Groups of 4 female rats were dosed orally with 500, 1000 or 2000 mg/kg ditridecylthiodipropionate. The test material was dissolved in corn oil. Animals were held for a minimum of two weeks.
Result	:	All animals survived two weeks after dosing with ditridecylthiodipropionate. All animals gained weight during the two week observation period.
Source	:	Pullin, T.G. and Schwebel, R.L. (1974). Acute toxicological properties and industrial handling of ... bis-(tridecylproprioonate) thioether. Unpublished Dow Chemical Company report.
Reliability	:	This study is assigned a reliability code of 2e according to the criteria established by Klimisch *et al.* (1997). It was not conducted under GLP or OECD guidelines but generally meets scientific standards, is well documented and is accepted for assessment.

5.1.2 ACUTE INHALATION TOXICITY

Type	:	LC0
Species	:	rat
Strain	:	
Sex	:	female
Number of animals	:	4
Vehicle	:	
Exposure time	:	
Method	:	
Year	:	1974
GLP	:	no
Test substance	:	as prescribed by 1.1 - 1.4
Method	:	Air flowed through a bubbler containing the test material at a

rate of 3 lpm. The air from the bubbler flowed through a chamber containing 4 female rats for 7 hours. Body weights of the rats were obtained immediately prior to the exposure and 1, 8 and 15 days post-exposure.

Result : The nominal concentration rats were exposed to was 0.19 mg/L. All animals survived the exposure and post-exposure recovery period. Body weights of the rats on day 1 post-exposure were comparable to pre-exposure values. Although one animal lost weight (5%) during the recovery period, the other three gained weight.

Source : Pullin, T.G. and Schwebel, R.L. (1974). Acute toxicological properties and industrial handling of ... bis-(tridecylproprioonate) thioether. Unpublished Dow Chemical Company report.

Reliability : This study is assigned a reliability code of 2e according to the criteria established by Klimisch *et al.* (1997). It was not conducted under GLP or OECD guidelines but generally meets scientific standards, is well documented and is accepted for assessment.

5.2 SKIN IRRITATION

Species : rabbit
Concentration :
Exposure :
Exposure time :
Number of animals :
PDII :
Result :
EC classification :
Method :
Year : 1974
GLP : no
Test substance : as prescribed by 1.1 - 1.4

Method : The fur is shaved from the abdomen of a rabbit. The animals are not used for several days to allow any abrasions to heal. Applications of 0.1 ml are applied to the tip of one ear on five days and are not covered. For the intact abdomen, 0.5 ml is applied under a cotton pad held in place with a cloth bandage for 24 hours. The material was applied 3 times. For the abraded abdomen, a small area of skin is scratched with a hypodermic needle to penetrate the stratum corneum. Three applications of 0.5 ml were made to the abraded skin. Each application was left in place for 24 hours.

All three sites, ear, intact abdomen and abraded abdomen, were observed after each application and graded. All three

sites were examined approximately one week after the last application.

Result : Ear: Moderate redness and necrosis were observed after 2 applications. Slight edema and exfoliation were also observed. The ear appeared to be normal 7 days after the last application.

Intact abdomen: Slight redness was observed after two applications to intact skin. Very slight edema was also observed. The skin remained the same three days after the last application. There was no evidence of redness or edema ten days after the last application. However, slight exfoliation was observed.

Abraded abdomen: Slight redness was observed after two applications to intact skin. Very slight edema was also observed. The skin appeared normal three days after the last application.

Source : Pullin, T.G. and Schwebel, R.L. (1974). Acute toxicological properties and industrial handling of ... bis-(tridecylproprioonate) thioether. Unpublished Dow Chemical Company report.

Reliability : This study is assigned a reliability code of 2e according to the criteria established by Klimisch *et al.* (1997). It was not conducted under GLP or OECD guidelines but generally meets scientific standards, is well documented and is accepted for assessment.

5.2.2 EYE IRRITATION

Species	:	rabbit
Concentration	:	undiluted
Dose	:	
Exposure Time	:	
Comment	:	
Number of animals	:	1
Result	:	
EC classification	:	
Method	:	
Year	:	1974
GLP	:	no
Test substance	:	as prescribed by 1.1 - 1.4

Method : Undiluted test material (0.1 ml) was instilled into each eye of one female rabbit. One eye was washed shortly after instillation of the test material while the other eye remained

unwashed. The animal was examined immediately and 1 and 24 hours after dosing for evidence of injury to the conjunctiva, cornea or iris.

Result : There was no evidence of pain noted in either eye of the rabbit following instillation of the test material. Similarly, there was no evidence of effects to the conjunctiva, cornea or iris in either eye of the animal.

Source : Pullin, T.G. and Schwebel, R.L. (1974). Acute toxicological properties and industrial handling of ... bis-(tridecylproprionate) thioether. Unpublished Dow Chemical Company report.

Reliability : This study is assigned a reliability code of 2e according to the criteria established by Klimisch *et al.* (1997). It was not conducted under GLP or OECD guidelines but generally meets scientific standards, is well documented and is accepted for assessment.

5.3 REPEATED DOSE TOXICITY

Estimated to have a 90-day NOAEL of ~350 mg/kg/day and a NOEL of ~125 mg/kg/day based on DLTDP (CAS#123-28-4).

Species : rat
Sex : 10 per sex per group (weeks 1-13); 5 per sex for the control and high dose treatment-free extension groups
Strain : Sprague-Dawley; 6 weeks of age at initiation of study.
Route of admin. : oral gavage
Body Weight Range : Males: 162-193 g; Females: 142-180g (at study initiation)
Exposure period : 13 weeks with a 4 week treatment-free period.
Frequency of treatment : daily
Post obs. period : yes, 4 weeks
Doses : 125, 350, and 1000 mg/kg/day
Control group : yes
Method : 13 Week Oral (gavage) Toxicity Study in the Rat followed by a 4 Week Treatment-free Period.
Summary Result : **NOAEL = 350 mg/kg/day; NOEL = 125 mg/kg/day**
Year : 1993
GLP : Yes
Test substance : **DLTDP (CAS#123-28-4)**
Method : Groups of 10 rats per sex per group were given doses of 0, 125, 350, or 1000 mg/kg/day by gavage, using a metal cannula for approximately 13 weeks. Dosing solutions were made daily and concentrations were analytically confirmed at weeks 1, 4, 8, and 13. Animals were housed in groups of 5 of the same sex and dose group per cage. The animal room was maintained at 19-25C, 35-75% relative humidity, and a 12 hour light/12 hour dark lighting cycle. Rats were fed ad lib, but

fasted ~16 hours prior to blood sampling, during the collection of urine, and before necropsy. Water was also provided ad lib, but withheld during urine collection. All animals were observed twice daily for morbidity and mortality. Clinical observations were done daily, with full clinical evaluations done weekly. Body weights and food consumption were recorded weekly. Opthalmoscopy was performed on all animals pretest and at week 13 in the control and high dose animals. Clinical pathology was performed on 10 animals/sex in control and high dose groups after week 4, 10 animals/sex in all groups after week 13, and in all recovery animals after week 17. Parameters included hematology (except on treatment-free period animals), blood clinical chemistry, and urinalysis. All animals were submitted to full necropsy. Organ weights were taken at necropsy. Histopathology was performed on all selected organs/tissues for all animals in the control and high dose groups, the liver, kidneys and lungs for all animals in all groups, and the heart from animals in groups 2 and 3 and in all recovery group animals. The hearts from all animals was examined after PTAH staining.

Remark : **Organs examined histologically also included the epidiymides, mammary glands, ovaries, prostate, seminal vesicles, testes, uterus (horn + cervix). This is suggestive of no adverse effects on reproduction.**

Result : There were no unscheduled deaths and no treatment related clinical signs. There were no treatment related differences in body weight gain and food consumption was unaffected by treatment. There were no treatment related eye lesions. None of the hematological parameters were considered to represent an adverse effect of treatment. None of the clinical chemistry parameters other than a reversible elevation in serum cholesterol in the high dose females and a reversible elevation of alanine and aspartate aminotransferase activities in all high dose animals were related to an effect of treatment. Urine parameters were unaffected other than being slightly more acidic in the high dose animals as compared to the controls. This was reversible after the 4 week treatment-free period. The minor differences in the weight of the major organs were considered of no toxicological significance in the absence of microscopic lesions. Macroscopic changes were considered to either be agonal or incidental in origin or unrelated to treatment. The treatment related microscopic lesions were seen in the heart of high dose animals. The lesion was described as small foci of degenerated or necrotic fibers associated with minimal to moderate mononuclear cell infiltration. This association suggested early or ongoing myocarditis. These lesions were not present in animals previously treated at the high dose level but allowed a 4 week

period without treatment. There were no other treatment related microscopic lesions.

In conclusion, the oral (gavage) administration of DLTDP to the rat for 13 weeks at a dose level of 1000 mg/kg/day was associated with a minor increase in serum cholesterol concentrations in females, increased serum ALAT and ASAT activities and decreased urinary pH in both sexes. Microscopic findings in the heart of these animals suggested on ongoing myocarditis. The heart was therefore identified as the target organ. All these changes were reversible after 4 weeks without treatment. At a dose level of 350 mg/kg/day there was no evidence for any microscopic change in the heart and not other differences to indicate an adverse effect of the test article. This dose level is therefore considered to be the no observed adverse effect level for DLTDP in the rat. There were no changes considered to represent an effect of the test article at 125 mg/kg/day and therefore this dose level is considered to be the no observed effect level for DLTDP in the rat.

Source : 13 Week Oral (gavage) Toxicity Study in the Rat followed by a 4 Week Treatment-free Period. Ciba-Geigy Ltd. Basel Switzerland. December 14, 1993.

Reliability : This study is assigned a reliability code of 1b according to the criteria established by Klimisch *et al.* (1997). It was conducted under GLP guidelines but uses a non-specified protocol method that generally meets scientific standards, is well documented and is acceptable for assessment.

5.4 GENETIC TOXICITY "IN VITRO" OR "IN VIVO"

Estimated to be Negative for bacterial mutagenicity based on DSTDP (CAS#693-36-7) and DLTDP (CAS# 123-28-4).

Estimated to be Negative for induction of chromosome aberrations based on DSTDP (CAS#693-36-7) and for DLTDP (CAS# 123-28-4).

Type : **Ames test**
System of testing :
Concentration : 33.3, 100, 333, 1000, 2500, 3333, 5000, 6667, and 10,000 ug/plate and 3.3 and 10 ug/plate for strain TA100
Cytotoxic conc. : No toxicity was observed at 10,000 ug/plate with and without metabolic activation.
Metabolic activation : with and without
Result : **negative**

Method	:	other: essentially follows OECD 471
Year	:	1979
GLP	:	no
Test substance	:	**DLTDP (CAS# 123-28-4)**
Method	:	Tested with and without metabolic activation using Salmonella typhimurium strains TA1535, TA1537, TA1538, TA98 and TA100 and Escherichia coli strain WP2. Liver S-9 fraction from Aroclor 1254 pretreated male Sprague-Dawley rats with NADPH generating system was used for metabolic activation. The experiment was repeated approximately 6 weeks later
Result	:	A precipitate was observed at the two highest doses tested. These plates were hand-counted. There was no evidence that it was mutagenic in the assays performed.
Flag	:	Critical study for SIDS endpoint
Source	:	SRI International (1979). Microbial mutagenesis testing of substances; compound report: F76-049, dilauryl thiodipropionate. NTIS report PB89169031.
Reliability	:	This study is assigned a reliability code of 1b according to the criteria established by Klimisch *et al.* (1997). It was not conducted under GLP guidelines but uses methods that generally meet scientific standards, is well documented and is acceptable for assessment.
Type	:	**Chromosome Aberration Cytogenetic Assay**
System of testing	:	Chinese Hamster V79 Cells
Concentration	:	0, 0.6, 0.75, 1.5, 3.0, 5.0 , 6.0 , 10.0 , 20.0 , 30.0 , 40.0 and 300.0 microg/ml
Cytotoxic conc.	:	In the absence of S9 mix reduced cell numbers to 55% of control were observed after treatment with 300 ug/ml whereas in the presence of S9 mix no toxic effects were observed.
Metabolic activation	:	with and without
Result	:	**negative**

OECD Guide-line 473 "Genetic Toxicology: In Vitro Mammalian Cytogenetic Test"

The test article, formulated in culture medium (MEM) was assessed for its potential to induce structural chromosome aberrations in V79 cells of the Chinese hamster in vitro in two independent experiments. The chromosomes were prepared 18 h ad 28 h after start of treatment with the test article. The treatment interval was 4 h (exp. I: without and with metabolic activation; exp II: with metabolic activation) or 18 h and 28 h without metabolic activation (exp.II). In each experimental group two parallel cultures were set up. Per culture, 100 metaphase plates were scored for chromosome aberrations.

The highest applied concentration in the pre-test was chosen with regard to the properties of the formulation of the test article. A homogenous suspension could be prepared at 300 ug/ml in the absence of S9 mix and 285 ug/ml in the presence of S9 mix. Test article concentrations between 1 and 300 ug/ml (-S9) or 1 and 285 ug/ml (+S9) were chosen for the assessment of the cytotoxic potential.
In the absence of S9 mix reduced cell numbers to 55% of control were observed after treatment with 300 ug/ml whereas in the presence of S9 mix no toxic effects were observed. In the pre-test precipitation of the test article was observed 4 h after start of treatment at concentrations of 5 ug/ml and above in the absence of S9 mix and 10 ug/ml and above in the presence of S9 mix.

In experiment I, test article concentrations within a range of 0.75 – 300 ug/ml (-S9 mix) and 0.6 – 20 ug/ml (+S9 mix) were applied for the investigation of the potential to induce cytogenetic damage. In experiment II, the applied test article concentration ranges were 0.75 – 300 ug/ml (-S9 mix) and 1.0 – 40 ug/ml (+S9 mix).

In the absence and the presence of S9 mix, in both experiments, no reduction of the mitotic index or the cell number was observed, except in the presence of S9 mix in experiment II at interval 28 h after treatment with 40 ug/ml reduced cell numbers were observed.

: In both independent experiments, neither a significant no a biologically relevant increase in the number of cells carrying structural chromosomal aberrations was observed after treatment with the test article.

In addition, no increase in the frequencies of polyploid metaphases was found after treatment with the test article as compared to the frequencies of the controls.

Appropriate mutagens (Ethylmethane sulfonate and Cyclophosphamide) were used as positive controls. They induced statistically significant increase in cells with structural chromosome aberrations.

In conclusion, under the conditions of this study, the test article did not induce structural chromosome aberrations and is considered to be non-mutagenic.

Year : 1998

GLP : yes

Test substance : **DSTDP (CAS#693-36-7)**

Source : In Vitro Chromosome Aberration Assay in Chinese Hamster V79 Cells with TK10594 (IRGANOX PS802). January 5, 1998

Reliability : This study is assigned a reliability code of 1a according to the criteria established by Klimisch *et al.* (1997). It was conducted under GLP and OECD guidelines, is well documented and is acceptable for assessment.

Type	:	**Salmonella typhimurium reverse mutation assay**
System of testing	:	Histidine-auxotrophic mutants of S. typhimurium, Strains TA98, TA100, and TA1537
Concentration	:	313 , 625 , 1250 , 2500 and 5000 microg/0.1 ml
Cytotoxic conc.	:	>5000 ug/0.1 ml
Metabolic activation	:	with and without
Result	:	**negative**
Method	:	The tests were carried out in accordance with the method described by Ames et al. 1973, 1973, and 1975. A preliminary toxicity test was carried out with strain TA100 without activation with the concentrations ranging from 20 to 5000 ug/0.1 ml. Accordingly, the concentration of 5000 ug/0.1 ml was used as the highest in the mutagenicity test and the tests were performed with the following concentrations of the trial substance without and with microsomal activations: 313, 625, 1250, 2500 and 5000 ug/0.1 ml.
	:	The test substance was dissolved in acetone. Acetone alone was used for the negative controls. The positive control substances were • 10 ug Daunorubicin-HCL/0.1 ml phosphate buffer for strain TA 98 • 0.25 ug 4-Nitroquinoline-N-oxide/0.1 ml DMSO for strain TA 100 • 100 ug 9(5)-Aminoacridine hydrochloride monohydrate/0.1 ml DMSO for strain TA 1537. • The activation mixture is tested with all strains and 5 ug 2-aminoanthracene/0.1 ml DMSO. In the experiments, three Petri dishes are prepared per strain/per concentration. Each Petri dish contains ~20 ml of agar solution plus salts and glucose, 0.1 ml of test solution and 0.1 ml of bacterial culture in 2.0 ml of soft agar. In those dishes with activation, 0.5 ml activation mixture is added. In the experiments performed, none of the tested concentrations led to an increase in the incidence of histidine-prototrophic mutants in comparisons with the controls.
Year	:	1989
GLP	:	No data
Test substance	:	**DSTDP (CAS#693-36-7)**
Source	:	Salmonella Mutagenicity Test with Three Strains with TK 10594 (IRGANOX PS 802). Ciba-Geigy Ltd. Basle, Switzerland. June 23, 1989.

Reliability	:	This study is assigned a reliability code of 2e according to the criteria established by Klimisch *et al.* (1997). It was not conducted under GLP or OECD guidelines but generally meets scientific standards, is well documented and is accepted for assessment.
Type	:	Dominant lethal assay
Species	:	rat
Sex	:	
Strain	:	no data
Route of admin.	:	gavage
Exposure period	:	an acute study and subacute study (dosed once/day for 5 days)
Doses	:	50, 500 or 5000 mg/kg
Result	:	negative
Method	:	other: essentially follows OECD 478
Year	:	1973
GLP	:	no
Test substance	:	**DLTDP (CAS# 123-28-4)**
Method	:	Male and female rats from a closed colony were used. Animals were 10-12 weeks old at the time of use. Ten male rats were assigned to each of 5 groups; 3 dose levels of dilauryl thiodipropionic acid, 50, 500 or 5000 mg/kg, a positive control, triethylene melamine, and a negative control group. The positive control was administered intraperitoneally at a dose level of 0.3 mg/kg. Administration of the test compound was orally by intubation in both the acute study and in the subacute study (dosed once/day for 5 days). Following treatment, the males were sequentially mated to 2 females/week for 8 weeks (7 weeks in the subacute study). Two virgin female rats were housed with a male for 5 days (Monday through Friday). These two females were removed and housed in a cage until sacrificed. The males were left alone for two days and two new females were housed with a male for the next 5 days (Monday through Friday). Females were killed using carbon dioxide at 14 days after separation from the male and at necropsy the uterus was examined for early deaths, late fetal deaths and total implantations.
Result	:	There was no clear pattern of either increases or decreases between the control and test groups in any of the parameters studied. Thus, dilauryl thiodipropionic acid was considered to be non-mutagenic in rats in the dominant lethal assay when using the dosages employed in this study.
Flag	:	Critical study for SIDS endpoint
Source	:	Litton Bionetics, Inc (1973) Mutagenic evaluation of compound FDA 71-40, dilauryl thiodipropionic acid. NTIS PB245452.

Reliability	:	This study is assigned a reliability code of 1b according to the criteria established by Klimisch *et al.* (1997). It was not conducted under GLP guidelines but uses methods that generally meet scientific standards, is well documented and is acceptable for assessment.
Type	:	**Micronucleus assay**
Species	:	rat
Sex	:	male
Strain	:	no data
Route of admin.	:	gavage
Exposure period	:	
Doses	:	
Result	:	**negative**
Method	:	other: essentially follows OECD 474 in vivo mammalian bone marrow micronucleus test
Year	:	1973
GLP	:	no
Test substance	:	**DLTDP (CAS# 123-28-4)**
Method	:	In the acute phase, groups of 5 male albino rats were sacrificed 6, 24 or 48 hours after dosing by oral gavage with 50, 500 or 5000 mg/kg dilauryl thiodipropionic acid. The negative control group of 9 rats received saline. The positive control group of 5 male rats received 0.3 mg/kg triethylene melamine and was sacrificed 48 hours after dosing. Two hours prior to each sacrifice, each animal received 4 mg/kg of colcemid intraperitoneally. Animals were sacrificed with carbon dioxide. The epiphysis of one femur was removed and the marrow aspirated into 5 ml of Hanks' balanced salt solution. The specimens were centrifuges at 1500 rpm for 5 minutes, decanted and 2 ml of hypotonic 0.5% KCl solution was aged with gentle agitation to resuspend the cells. The specimens were then placed in a 37C water bath for 20 minutes in order to swell the cells. Following centrifugation for 5 minutes at 1500 ppm, the supernatant was decanted and 2 ml of fixative (3:1 absolute methanol:glacial acetic acid) was added. The cells were resuspended in the fixative with gentile agitation, capped and maintained at 4C for 30 minutes. The specimens were again centrifuged, decanted, 2 ml of prepared fixative was added, and the cells were resuspended and maintained at 4C overnight. Cells were placed on a slide and stained with a 5% Giemsa solution for 20 minutes, rinsed in acetone, 1:1 acetone:xylene, and placed in fresh xylene for 30 minutes. Fifty metaphase spreads were scored per animal. Mitotic indices were obtained by counting at least 500 cells and the ratio of the number of cells in mitosis/the number of cells observed was expressed as the mitotic index.
Result	:	The compound produced no detectable significant aberration

of the bone marrow metaphase chromosomes of rats when administered orally at the dosage levels employed in this study following acute or short term exposure.

Flag : Critical study for SIDS endpoint

Source : Litton Bionetics, Inc (1973) Mutagenic evaluation of compound FDA 71-40, dilauryl thiodipropionic acid. NTIS PB245452.

Reliability : This study is assigned a reliability code of 1b according to the criteria established by Klimisch *et al.* (1997). It was not conducted under GLP guidelines but uses methods that generally meet scientific standards, is well documented and is acceptable for assessment.

Type : other: host mediated assay
Species : mouse
Sex : male
Strain : ICR
Route of admin. : gavage
Exposure period : 3 hours
Doses : 50, 500 or 5000 mg/kg
Result : ambiguous
Method :
Year : 1973
GLP : no
Test substance : **DLTDP (CAS# 123-28-4)**
Method : Groups of 10 ICR random-bred male mice were used in the acute and subacute studies. Dilauryl thiodipropionic acid was administered orally by intubation at doses of 50, 500 or 5000 mg/kg. The positive control group received either 100 mg/kg dimethylnitrosamine in the case of Salmonella or 350 mg/kg ethylmethane sulfonate in the case of Saccharomyces. All animals received 2 ml of the indicator organism intraperitoneally. Each ml contained 3.0 x 10 8 cells of Salmonella (his G-46 and TA-1530) and 5.0 x 108 cells of Saccharomyces (D-3). Three hours later each animal was sacrificed and 2 ml sterile saline introduced intraperitoneally. As much fluid as possible was then aseptically removed from the peritoneal cavity. Tenfold serial dilutions were made of each peritoneal exudate yielding a concentration series from 100 through 10-7. For enumeration of total bacterial counts, the 10-6 and 10-7 dilutions were plated on tryptone yeast extract agar. In plating for the total mutant counts on minimal agar, the 100 dilution was used. The plating procedure was identical to that followed for the tryptone yeast extract agar plates. All plates were incubated at 37C, tryptone yeast extract plates for 18 hours and minimal agar plates for 40 hours. For yeast mitotic recombination, ten-fold serial dilutions were made of each sample yielding a series from 100 to 10-5.

Samples of 0.1 ml of the 10-5, 10-4, and 10-3 dilutions were removed and plated on complete medium (10 plates each). All plates were incubated at 30C for 40 hours. The 10-5 dilutions were used to determine total populations and 10-4 and 10-3 plates were examined after an additional 40 hours at 4C for mutations. Mutations were seen as red colonies or as red sectors on a normally white yeast colony.

Result : Dilauryl thiodipropionic acid produced no significant reversion or recombinant increases in Salmonella strain TA-1530 or Saccharomyces strain D-3, respectively. The results from tests using Salmonella strain G-46 indicated that this compound induced reversion in both the acute and subacute trials. A slight dose response was observed in the acute trials (0.54, 2.11, 4.51 and 5.36 in the control, 50, 500 and 5000 mg/kg groups, respectively) but not in the subacute trials (0.62, 5.62, 6.03 and 6.33 in the control, 50, 500 and 5000 mg/kg groups respectively). Repeat tests of the acute trials indicated the compound induced reversion, although the results were not dose dependent (5.42, 6.82 and 5.99 in the 50, 500 and 5000 mg/kg group, respectively).

Source : Litton Bionetics, Inc (1973) Mutagenic evaluation of compound FDA 71-40, dilauryl thiodipropionic acid. NTIS PB245452.

Reliability : This study is assigned a reliability code of 2e according to the criteria established by Klimisch *et al.* (1997). It was not conducted under GLP or OECD guidelines but uses methods that generally meet scientific standards, is well documented and is acceptable for assessment.

5.5 TOXICITY TO REPRODUCTION

Based on the results of the 90-day repeat dose study in DLTDP (CAS#123-28-4). Results of this study indicated there were no macro or microscopic changes in any of the male or female reproductive organs. Thus suggestive that at the doses tested the material would not be a reproductive toxicant. Based on this it is estimated that this material would not be a reproductive toxicant.

Species : rat
Sex : 10 per sex per group (weeks 1-13); 5 per sex for the control and high dose treatment-free extension groups
Strain : Sprague-Dawley; 6 weeks of age at initiation of study.
Route of admin. : oral gavage
Body Weight Range : Males: 162-193 g; Females: 142-180g (at study initiation)
Exposure period : 13 weeks with a 4 week treatment-free period.
Frequency of treatment : daily

Post obs. period	:	yes, 4 weeks
Doses	:	125, 350, and 1000 mg/kg/day
Control group	:	yes
Method	:	13 Week Oral (gavage) Toxicity Study in the Rat followed by a 4 Week Treatment-free Period.
Summary Result	:	**NOAEL = 350 mg/kg/day; NOEL = 125 mg/kg/day**
Year	:	1993
GLP	:	Yes
Test substance	:	**DLTDP (CAS#123-28-4)**
Method	:	Groups of 10 rats per sex per group were given doses of 0, 125, 350, or 1000 mg/kg/day by gavage, using a metal cannula for approximately 13 weeks. Dosing solutions were made daily and concentrations were analytically confirmed at weeks 1, 4, 8, and 13. Animals were housed in groups of 5 of the same sex and dose group per cage. The animal room was maintained at 19-25C, 35-75% relative humidity, and a 12 hour light/12 hour dark lighting cycle. Rats were fed ad lib, but fasted ~16 hours prior to blood sampling, during the collection of urine, and before necropsy. Water was also provided ad lib, but withheld during urine collection. All animals were observed twice daily for morbidity and mortality. Clinical observations were done daily, with full clinical evaluations done weekly. Body weights and food consumption were recorded weekly. Opthalmoscopy was performed on all animals pretest and at week 13 in the control and high dose animals. Clinical pathology was performed on 10 animals/sex in control and high dose groups after week 4, 10 animals/sex in all groups after week 13, and in all recovery animals after week 17. Parameters included hematology (except on treatment-free period animals), blood clinical chemistry, and urinalysis. All animals were submitted to full necropsy. Organ weights were taken at necropsy. Histopathology was performed on all selected organs/tissues for all animals in the control and high dose groups, the liver, kidneys and lungs for all animals in all groups, and the heart from animals in groups 2 and 3 and in all recovery group animals. The hearts from all animals was examined after PTAH staining.
Remark	:	**Organs examined histologically also included the epidiymides, mammary glands, ovaries, prostate, seminal vesicles, testes, uterus (horn + cervix). This is suggestive of no adverse effects on reproduction.**
Result	:	There were no unscheduled deaths and no treatment related clinical signs. There were no treatment related differences in body weight gain and food consumption was unaffected by treatment. There were no treatment related eye lesions. None of the hematological parameters were considered to represent an adverse effect of treatment. None of the clinical chemistry parameters other than a reversible elevation in serum

cholesterol in the high dose females and a reversible elevation of alanine and aspartate aminotransferase activities in all high dose animals were related to an effect of treatment. Urine parameters were unaffected other than being slightly more acidic in the high dose animals as compared to the controls. This was reversible after the 4 week treatment-free period. The minor differences in the weight of the major organs were considered of no toxicological significance in the absence of microscopic lesions. Macroscopic changes were considered to either be agonal or incidental in origin or unrelated to treatment. The treatment related microscopic lesions were seen in the heart of high dose animals. The lesion was described as small foci of degenerated or necrotic fibers associated with minimal to moderate mononuclear cell infiltration. This association suggested early or ongoing myocarditis. These lesions were not present in animals previously treated at the high dose level but allowed a 4 week period without treatment. There were no other treatment related microscopic lesions.

In conclusion, the oral (gavage) administration of DLTDP to the rat for 13 weeks at a dose level of 1000 mg/kg/day was associated with a minor increase in serum cholesterol concentrations in females, increased serum ALAT and ASAT activities and decreased urinary pH in both sexes. Microscopic findings in the heart of these animals suggested on ongoing myocarditis. The heart was therefore identified as the target organ. All these changes were reversible after 4 weeks without treatment. At a dose level of 350 mg/kg/day there was no evidence for any microscopic change in the heart and not other differences to indicate an adverse effect of the test article. This dose level is therefore considered to be the no observed adverse effect level for DLTDP in the rat. There were no changes considered to represent an effect of the test article at 125 mg/kg/day and therefore this dose level is considered to be the no observed effect level for DLTDP in the rat.

Source : 13 Week Oral (gavage) Toxicity Study in the Rat followed by a 4 Week Treatment-free Period. Ciba-Geigy Ltd. Basel Switzerland. December 14, 1993.

Reliability : This study is assigned a reliability code of 1b according to the criteria established by Klimisch *et al.* (1997). It was conducted under GLP guidelines but uses a non-specified protocol method that generally meets scientific standards, is well documented and is acceptable for assessment.

5.6 DEVELOPMENTAL TOXICITY/TERATOGENICITY

Based on the results of teratogenicity assays in four species using DLTDP (CAS#123-28-4) it is estimated that this material would not be a teratogen.

Species	:	**rat**
Sex	:	female
Strain	:	Wistar
Route of admin.	:	gavage
Exposure period	:	
Frequency of treatment	:	
Duration of test	:	
Doses	:	16, 74, 350 or 1600 mg/kg
Control group	:	yes
NOAEL Maternalt.	:	**= 1600 mg/kg bw**
NOAEL Teratogen	:	**= 1600 mg/kg bw**
Method	:	other: essentially follows OECD 414
Year	:	1972
GLP	:	no
Test substance	:	**DLTDP (CAS#123-28-4)**
Method	:	A positive control group received 250 mg/kg aspirin. Frequency of treatment for positive control group not stated. The number of pregnant rats at the end of the study ranged from 19-21/dose level. Feed and water were available ad libitum. The rats were observed daily for general appearance and behavior, with emphasis on feed consumption and weight. Weights were obtained on days 0, 6, 11, 15 and 20 of gestation. On day 20 of gestation caesarian sections were performed and the numbers of implantation and resorption sites as well as the numbers of live and dead fetuses were recorded. The urogenital tract of each dam was examined for any abnormality, all fetuses were examined for any gross external abnormalities, and all live pups were weighed. Visceral examinations were performed on one-third of the fetuses of each litter, and the remaining two-thirds were examined for skeletal defects.
Result	:	No adverse effects with respect to number of implantations and maternal or fetal death were noted after oral administration to rats of up to 1600 mg/kg dilauryl thiodipropionic acid on days 6-15 of gestation. There were no significant differences in numbers of abnormalities of the soft or skeletal tissues between the treated and sham control fetuses.
Flag	:	Critical study for SIDS endpoint
Source	:	Food and Drug Research Labs, Inc. (FDRL). (Dec. 29, 1972). Teratologic evaluation of FDA 71-40 (Dilauryl thiodipropionic acid) in mice, rats, and hamsters. Springfield, VA: U.S.

Department of Commerce, National Technical Information Service (NTIS). NTIS publication #PB221 77.

Reliability	:	This study is assigned a reliability code of 1b according to the criteria established by Klimisch *et al.* (1997). It was not conducted under GLP guidelines but uses methods that generally meet scientific standards, is well documented and is acceptable for assessment.
Species	:	**mouse**
Sex	:	female
Strain	:	CD-1
Route of admin.	:	gavage
Exposure period	:	days 6-15
Frequency of treatment	:	daily
Duration of test	:	
Doses	:	16, 74, 350 and 1600 mg/kg
Control group	:	yes
NOAEL Maternalt.	:	**= 1600 mg/kg bw**
NOAEL Teratogen	:	**= 1600 mg/kg bw**
Method	:	other: essentially follows OECD 414
Year	:	1972
GLP	:	no
Test substance	:	**DLTDP (CAS#123-28-4)**
Method	:	A positive control group received 150 mg/kg aspirin. Frequency of treatment for the positive control not stated. The number of pregnant mice at the end of the study ranged from 20-22/dose level. Feed and water were available ad libitum. The mice were observed daily for general appearance and behavior, with emphasis on feed consumption and weight. Weights were obtained on days 0, 6, 11, 15 and 17 of gestation. On day 17 of gestation caesarian sections were performed and the numbers of implantation and resorption sites as well as the numbers of live and dead fetuses were recorded. The urogenital tract of each dam was examined for any abnormality, all fetuses were examined for any gross external abnormalities, and all live pups were weighed. Visceral examinations were performed on one-third of the fetuses of each litter, and the remaining two-thirds were examined for skeletal defects.
Result	:	No adverse effects were found with respect to implantations and maternal and fetal survival after oral administration to mice of up to 1600 mg/kg TDPA on days 6-15 of gestation. The number of abnormalities seen in the soft or skeletal tissues of the treated fetuses was comparable to that seen in the sham control fetuses.
Source	:	Food and Drug Research Labs, Inc. (FDRL). (Dec. 29, 1972). Teratologic evaluation of FDA 71-40 (Dilauryl thiodipropionic

acid) in mice, rats, and hamsters. Springfield, VA: U.S. Department of Commerce, National Technical Information Service (NTIS). NTIS publication #PB221 77.

Reliability	:	This study is assigned a reliability code of 1b according to the criteria established by Klimisch *et al.* (1997). It was not conducted under GLP guidelines but uses methods that generally meet scientific standards, is well documented and is acceptable for assessment.
Species	:	**rabbit**
Sex	:	female
Strain	:	Dutch
Route of admin.	:	gavage
Exposure period	:	days 6-18 of gestation
Frequency of treatment	:	daily
Duration of test	:	
Doses	:	2.5, 10, 45, 216, 1000 mg/kg
Control group	:	yes
NOAEL Maternalt.	:	**= 1000 mg/kg bw**
NOAEL Teratogen	:	**= 1000 mg/kg bw**
Method	:	other: essentially follows OECD 414
Year	:	1973
GLP	:	no
Test substance	:	**DLTDP (CAS#123-28-4)**
Method	:	Groups of 15-29 artificially inseminated females/dose level resulted in 8-13 pregnant rabbits/dose level. On day 29, all does were subjected to c-section. The numbers of corpora lutea, implantation sites, resorption sites, and live and dead fetuses recorded. The body weights of the live pups were also recorded. The urogenital tract of each animal was examined in detail for normality. All fetuses underwent a detailed gross examination for the presence of external congenital abnormalities. The live fetuses of each litter were then placed in an incubator for 24 hours for the evaluation of neonatal survival. All surviving pups were sacrificed, and all pups examined for visceral abnormalities by dissection. All fetuses were then cleared in potassium hydroxide, stained with alizarin red S dye and examined for skeletal defects.
Result	:	Eight to thirteen pregnant dams survived to term. There was no clearly discernible effect on nidation or on maternal or fetal survival at doses as high as 1000 mg/kg. The number of abnormalities seen in either soft or skeletal tissues of the test groups did not differ from the number occurring spontaneously in the control
Flag	:	Critical study for SIDS endpoint
Source	:	FDA (1973). Teratologic evaluation of FDA 71-40 (dilauryl thiodipropionic acid) NTIS PB-223 824.

Reliability	:	This study is assigned a reliability code of 1b according to the criteria established by Klimisch *et al.* (1997). It was not conducted under GLP guidelines but uses methods that generally meet scientific standards, is well documented and is acceptable for assessment.
Species	:	**hamster**
Sex	:	female
Strain	:	other: golden
Route of admin.	:	gavage
Exposure period	:	Day 6-10 of gestation
Frequency of treatment	:	daily
Duration of test	:	
Doses	:	16, 74, 350 or 1600 mg/kg
Control group	:	yes
NOAEL Maternalt.	:	**= 1600 mg/kg bw**
NOAEL Teratogen	:	**= 1600 mg/kg bw**
Method	:	other: essentially follows guideline 414
Year	:	1972
GLP	:	no
Test substance	:	**DLTDP (CAS#123-28-4)**
Method	:	The number of hamsters at the end of the study ranged from 20-23/dose level. Feed and water were available ad libitum. The hamsters were observed daily for general appearance and behavior, with emphasis on feed consumption and weight. Weights were obtained on days 0, 8, 10 and 14 of gestation. On day 14 of gestation caesarian sections were performed and the numbers of implantation and resorption sites as well as the numbers of live and dead fetuses were recorded. The urogenital tract of each dam was examined for any abnormality, all fetuses were examined for any gross external abnormalities, and all live pups were weighed. Visceral examinations were performed on one-third of the fetuses of each litter, and the remaining two-thirds were examined for skeletal defects.
Result	:	The numbers of implantations and maternal and fetal survival were not adversely affected by oral administration to hamsters of up to 1600 mg/kg TDPA on days 6-10 of gestation. No significant differences in the number of soft or skeletal tissue abnormalities were found between treated and sham control fetuses.
Source	:	Food and Drug Research Labs, Inc. (FDRL). (Dec. 29, 1972). Teratologic evaluation of FDA 71-40 (Dilauryl thiodipropionic acid) in mice, rats, and hamsters. Springfield, VA: U.S. Department of Commerce, National Technical Information Service (NTIS). NTIS publication #PB221 77.
Reliability	:	This study is assigned a reliability code of 1b according to the

criteria established by Klimisch *et al.* (1997). It was not conducted under GLP guidelines but uses methods that generally meet scientific standards, is well documented and is acceptable for assessment.

Blok, J., de Morsier, AA., Gerike, P., Reynolds, L. and Wellens, H. (1985). Harmonisation of ready biodegradability tests. Chemosphere 14:1805-1820.

Cytec (05/21/1999) Cyanox 711 antioxidant. Cytec MSDS

Dow Chemical Co. (09/14/99). Ditridecyl thiodipropionate. Dow Chemical Co. MSDS.

FDA (1973). Teratologic evaluation of FDA 71-40 (dilauryl thiodipropionic acid) NTIS PB-223 824.

Food and Drug Research Labs, Inc. (FDRL). (Dec. 29, 1972). Teratologic evaluation of FDA 71-40 (Dilauryl thiodipropionic acid) in mice, rats, and hamsters. Springfield, VA: U.S. Department of Commerce, National Technical Information Service (NTIS). NTIS publication #PB221 77.

Hampshire MSDS (09-14-99). Ditridecyl thiodipropionate MSDDS.

In Vitro Chromosome Aberration Assay in Chinese Hamster V79 Cells with TK10594 (IRGANOX PS802). January 5, 1998

Klimisch, H.J., Andreae, M and Tillman, U. A systemic approach for evaluating the quality of experimental toxicological and ecotoxicological data. *Regulatory Toxicology and Pharmacology*. 25: 1-5, 1997.

Litton Bionetics, Inc (1973) Mutagenic evaluation of compound FDA 71-40, dilauryl thiodipropionic acid. NTIS PB245452.

Pullin, T.G. and Schwebel, R.L. (1974). Acute toxicological properties and industrial handling of ... bis-(tridecylproprioonate) thioether. Unpublished Dow Chemical Company report.

Report on the 13 Week Oral (gavage) Toxicity Study in the Rat followed by a 4 Week Treatment-free Period. Ciba-Geigy Ltd. Basel Switzerland. December 14, 1993.

Report on the Growth Inhibition Test of IRGANOX PS 800 to Green Algae (Scenedesmus subspicatus), Ciba-Geigy Ltd. Basle, Switzerland. September 16, 1992.

Report on the Test for Acute Toxicity of TK10030 to Daphnia Magna, Ciba-Geigy Ltd. Basle, Switzerland. November 25, 1988.

Report on the Test for Acute Toxicity of TK10030 to Zebra-Fish, Ciba-Geigy Ltd. Basle, Switzerland. December 2, 1988.

Report on the Test for Ready Biodegradability of TK10030 in the Modified Sturm Test, Ciba-Geigy Ltd. Basle, Switzerland. February 21, 1989.

Salmonella Mutagenicity Test with Three Strains with TK 10594 (IRGANOX PS 802). Ciba-Geigy Ltd. Basle, Switzerland. June 23, 1989.

SRI International (1979). Microbial mutagenesis testing of substances; compound report: F76-049, dilauryl thiodipropionate. NTIS report PB89169031.

Syracuse Research Corporation, Syracuse, NY and U.S. Environmental Protection Agency, Office of Pollution Prevention and Toxics (2000)

7. Klimisch Evaluation

Id 10595-72-9
Date 02/03/03

Klimisch, H.J., Andreae, M and Tillman, U. A systemic approach for evaluating the quality of experimental toxicological and ecotoxicological data. *Regulatory Toxicology and Pharmacology*. 25: 1-5, 1997.

1 = Valid without restriction

1a: GLP guideline study
1b: Comparable to guideline study
1c: Meets national standard methods (AFNOR/DIN)
1d: Meets generally accepted scientific standards and is described in sufficient detail

2 = Valid with restriction

2a: Guideline study without detailed documentation
2b: Guideline study with acceptable restrictions
2c: Comparable to guideline study with acceptable restrictions
2d: Meets national standard methods with acceptable restrictions
2e: Meets generally accepted scientific standards, well-documented and acceptable for assessment
2f: Accepted calculation method
2g: Data from Handbook or collection of data

3 = Invalid

3a: Documentation insufficient for assessment
3b: Significant methodological deficiencies
3c: Unsuitable test system

4 = Insufficient Documentation

4a: Abstract
4b: Secondary literature
4c: Original reference not yet available
4d: Original reference in foreign language
4e: Documentation insufficient for assessment

IUCLID

Data Set

Existing Chemical : ID: 123-28-4
CAS No. : 123-28-4

COMPANY INFORMATION

Name of Producer : Hampshire Chemical Corp., a wholly owned subsidiary of The Dow Chemical Company.
Street : 45 Hayden Ave. Suite 2500
Town : Lexington, MA 02421-7994
Country : United States

Name of Producer : Cytec Industries Inc.
Street : 5 Garret Mountain Plaza
Town : West Paterson, NJ 07424
Country : United States

Name of Producer : Crompton Corporation
Street : One American Lane
Town : Greenwich, CT 06831
Country : United States

1.1 GENERAL SUBSTANCE INFORMATION

Substance type	: organic
Physical status	: solid
Purity	: > 97 % w/w
Remark	: Material is a white solid (powder or flakes).
Reference	Hampshire MSDS (3-31-97). Dilauryl thiodipropionate MSDS

1.2 SYNONYMS

Propanoic acid, 3,3'-thiobis-, didodecyl ester
3,3'-Thiodipropionate de didodecyle
didodecyl 3,3'-thiodipropionate
Didodecyl-3,3'-thiodipropionat (German)
3,3'-tiodipropionato de didodecilo (Spanish)
Propanoic acid, 3,3'-thiobis-, didodecyl ester
Dilauryl thiodipropionate
Propanoic acid, 3,3'-thiobis-, didodecyl ester
3,3'-THIODIPROPIONSAEURE-DIDODECYLESTER (German)
DILAURYL 3,3'-THIODIPROPIONATE
Propanoic acid, 3,3'-thiobis-,didodecyl ester
DIPROPIONATE, 3,3'-THIO-, DIDODECYL

OTHER NAME(S):
Advastab 800
Antiox DLTP
Antiox L
Antioxidant AS
Antioxidant LTDP
Arbestab DLTP
Bis(dodecyloxycarbonylethyl) sulfide
Carstab DLTDP
Cyanox LTDP
D 1
D 1 (antioxidant)
Dilauryl b,b'-thiodipropionate
Dilauryl b-thiodipropionate
DLT
DLTDP
DLTP
DMPTP
Evanstab 12
Hostanox SE 1
Ipognox 89
Irgafos PS 800
IRGANOX PS 800

Lauryl 3,3'-thiodipropionate
Lusmit
Milban F
Neganox DLTP
Nocrac 400
Nonox DLTDP
Plastanox LTDP
Plastanox LTDP Antioxidant
Propionic acid, 3,3'-thiobis-, didodecyl ester
Propionic acid, 3,3'-thiodi-, didodecyl ester
PS 800
Rasumitto
Stabilizer DLT
Sumilizer TPL
Sumilizer TPL-R
Thiobis(dodecyl propionate)
Thiodipropionic acid didodecyl ester
TPL
TPL-R
Tyox B

1.3 IMPURITIES

CAS-No	:	112-53-8
EINECS-No	:	203-982-0
EINECS-Name	:	dodecan-1-ol
Contents	:	< 3 % w/w
Reference		Hampshire MSDS (3-31-97). Dilauryl thiodipropionate MSDS

2.1MELTING POINT

Value	:	**= 40 ° C**
Method	:	
Year	:	1977
GLP	:	no
Test substance	:	as prescribed by 1.1 – 1.4
Source	:	Hawley, G.G. (1977). The Condensed Chemical Dictionary, 9th Ed. New York: Van Nostrand Reinhold CO.
Reliability	:	Values from a collection of data are assigned a reliability code of 2g according to the criteria established by Klimisch *et al.* (1997).

2.2BOILING POINT

Test substance	:	as prescribed by 1.1 - 1.4
Remark	:	Boiling point is not applicable. Test material decomposes at >300C.

2.3VAPOUR PRESSURE

Value	:	**6.51E-9 mmHg at 25° C**
Decomposition	:	
Method		other (calculated): MPBPWIN version 1.40
Year	:	2001
GLP	:	Not applicable for calculated values
Test substance	:	as prescribed by 1.1 - 1.4
Source	:	Estimated by the MPBPWIN Program (v.1.40), using Modified Grain Method. Syracuse Research Corporation, Syracuse, NY and U.S. Environmental Protection Agency, Office of Pollution Prevention and Toxics (2000).
Reliability	:	The vapor pressure determination from an accepted calculation method is assigned a reliability code of 2f according to the criteria established by Klimisch *et al.* (1997).

Value	:	= **.2666 hPa at 163° C**
Decomposition	:	
Method		
Year	:	
GLP	:	
Test substance	:	as prescribed by 1.1 - 1.4
Source	:	CYTEC MSDS (9/01/98). Cyanox LTDP Antioxidant MSDS.
Reliability	:	Values from a collection of data are assigned a reliability code of 2g according to the criteria established by Klimisch *et al.* (1997).

Value	:	= **4.4 hPa at 230° C**
Decomposition	:	
Method		
Year	:	
GLP	:	no
Test substance	:	as prescribed by 1.1 - 1.4
Source	:	Hampshire MSDS (3-31-97). Dilauryl thiodipropionate MSDS
Reliability	:	Values from a collection of data are assigned a reliability code of 2g according to the criteria established by Klimisch *et al.* (1997).

2.4 PARTITION COEFFICIENT

Log Pow	:	**= 11.79 at 25° C**
Method		other (calculated): KOWWIN Program v1.66
Year	:	2001
GLP	:	Not applicable for calculated values
Test substance	:	as prescribed by 1.1 - 1.4
Source	:	Estimated by the KowWin Program (v.1.66) Syracuse Research Corporation, Syracuse, NY and U.S. Environmental Protection Agency, Office of Pollution Prevention and Toxics (2000).
Reliability	:	The partition coefficient determined from an accepted calculation method is assigned a reliability code of 2f according to the criteria established by Klimisch *et al.* (1997).

2.5 WATER SOLUBILITY

Value	:	= **4.94E-8 mg/l at 25 ° C**
Qualitative	:	
Pka	:	at 25 ° C
PH	:	at and ° C
Method	:	other: (calculated) WSKOW version 1.40
Year	:	2001
GLP	:	Not applicable for calculated values
Test substance	:	as prescribed by 1.1 - 1.4
Source	:	Estimated from Kow with WSKOW (v1.40) : KowWin Estimate Syracuse Research Corporation, Syracuse, NY and U.S. Environmental Protection Agency, Office of Pollution Prevention and Toxics (2000).
Reliability	:	The water solubility determined from an accepted calculation method is assigned a reliability code of 2f according to the criteria established by Klimisch *et al.* (1997).

Value	:	
Qualitative	:	**insoluble (< 0.1 mg/L)**

2. Physical Chemistry

Id 123-28-4
Date 01/14/03

Pka	:	
PH	:	
Method	:	
Year	:	
GLP	:	no
Test substance	:	as prescribed by 1.1 - 1.4
Source	:	Hampshire MSDS (3-31-97). Dilauryl thiodipropionate MSDS
Reliability	:	Values from a collection of data are assigned a reliability code of 2g according to the criteria established by Klimisch *et al.* (1997).

3.1.1 PHOTODEGRADATION

Type	:	air
Light source	:	
Light spect.	:	nm
Rel. intensity	:	based on Intensity of Sunlight
Direct photolysis		
Half-life t1/2	:	**= 2.5 hour(s)**
		For reaction with hydroxyl radicals, the predicted half-life of the chemical is relatively rapid
Degradation	:	% after
Quantum yield	:	
Indirect photolysis		
Sensitizer	:	
Conc. of sens.	:	
Rate constant	:	**= 52.0771 E-12 cm3/(molecule*sec)**
Degradation	:	% after
Deg. Product	:	
Method	:	other (calculated): AOP version 1.90
Year	:	2001
GLP	:	Not applicable for calculated values
Test substance	:	as prescribed by 1.1 - 1.4
Source	:	Estimated by the AOP program (v1.90), which estimates rate constants and half-lives of atmospheric reactions of organic compounds with hydroxyl radicals and ozone in the atmosphere. Syracuse Research Corporation, Syracuse, NY and U.S. Environmental Protection Agency, Office of Pollution Prevention and Toxics (2000).
Reliability	:	Photodegradation determined from an accepted calculation method is assigned a reliability code of 2f according to the criteria established by Klimisch *et al.* (1997).

3.1.2 STABILITY IN WATER

Not Applicable: Due to Insolubility of Material.

3.3.1 TRANSPORT BETWEEN ENVIRONMENTAL COMPARTMENTS

MacKay Level III Fugacity Model

Medium	Concentration %	Emissions (kg/hr)
Air	**0.282**	**1000**
Water	**7.02**	**1000**
Soil	**30.4**	**1000**
Sediment	**62.3**	**0**
Persistence Time		**654 hr**

Medium	Concentration %	Emissions (kg/hr)
Air	**5.31**	**1000**
Water	**2.14**	**0**
Soil	**73.6**	**0**
Sediment	**19**	**0**
Persistence Time		**105 hr**

Medium	Concentration %	Emissions (kg/hr)
Air	**8.03e-10**	**0**
Water	**10.1**	**1000**
Soil	**1.11e-8**	**0**
Sediment	**89.9**	**0**
Persistence Time		**1.34e+3 hr**

Medium	Concentration %	Emissions (kg/hr)
Air	**4.51e-12**	**0**
Water	**1.36e-3**	**0**
Soil	**100**	**1000**
Sediment	**2.1e-2**	**0**
Persistence Time		**520 hr**

Source : Estimated by the Level III Fugacity Model (Full-Output)

Syracuse Research Corporation, Syracuse, NY and U.S. Environmental Protection Agency, Office of Pollution Prevention and Toxics (2000).

Reliability : The fugacity determined from an accepted calculation method is assigned a reliability code of 2f according to the criteria established by Klimisch *et al.* (1997).

3.5 BIODEGRADATION

Type : Aerobic
Inoculum : Bacteria collected from activated sludge of the sewage treatment plant of CH – 4153 Reinach on 2/1/89.
Contact time : 28 days
Degradation : = 25 % after 28 day (10.9 mg test substance/L)
= 57 % after 28 day (19.9 mg test substance/L)
Result : **Not Readily Biodegradable**

Method : OECD Guide-line 301 B "Ready Biodegradability: Modified Sturm Test (CO2 evolution)"

- 2-liter flasks equipped with gas inlet and magnetic stirrers were used as the test vessels. The test medium was prepared according to the method described in the guideline. The temperature was maintained at 22 ± 2 °C, 28 days. Aeration consisted of ~ 25 ml/min air free of carbon dioxide.
- Reference Substance: 20 mg/L with 0.5 ml of the nonylphenol 10EO5PO.
- Test Substance: 10.9 mg/L and 19.9 mg/L
- 1200 ml of the mineral solution with the inoculum was aerated for 24 hours in the test vessel. In 300 ml mineral solution 0.5 ml nonylphenol 10EO5PO (solution of 30 mg in 100 ml bidist. Water) and 16.3 rsp. 29.9 mg of test substance were added and homogenized. This solution was given to the test vessel which was immediately connected to the CO2 traps.
- Blank: Water as specified in the guideline containing 0.5 ml of the nonylphenol 10EO5PO solution.
- Measurements: Determination of the initial CO2 of the 0.05 N sodium hydroxide and the CO2, absorbed in the absorbers filled with 200 ml 0.05 N sodium hydroxide on the days 6, 10, 13, 17, 20 (only for blank and reference), 21, 24, 27, and 28.
- The biodegradation was calculated on the basis of the theoretical carbon content of the test substance and the cumulative quantities of carbon dioxide determined on the days of measurements. For the calculation the formula given in the guideline was used.
- Reference Substance Biodegradation: 20 mg/L = 84.3% in 28 days.
- Test Substance: 10.87 mg/L = 25% in 28 days & 19.93 mg/L = 57% in 28 days.

Year : 1989
GLP : In spirit of GLP
Test substance : as prescribed by 1.1 - 1.4
Remark : Due to the poor solubility of the test material in water, an emulsifier was used to achieve a better distribution in the

medium. The test substance was added to the medium, homogenized with nonylphenol 10EO5PO.

The volume of the test solution was reduced from 3L to 1.5L. The CO2 formed by biodegradation was absorbed with NaOH and determined on a carbon analyzer.

Source : Report on the Test for Ready Biodegradability of TK10030 in the Modified Sturm Test, Ciba-Geigy Ltd. Basle, Switzerland. February 21, 1989.

Reliability This study is assigned a reliability code of 1b according to the criteria established by Klimisch et al. (1997). It was conducted under OECD guidelines.

4.1 ACUTE/PROLONGED TOXICITY TO FISH

Type	:	OECD Guideline 203
Species	:	Zebra-Fish (Brachydanio rerio)
Exposure period	:	96 hour(s)
Unit	:	mg/l
Analytical monitoring	:	yes
LC50	:	**>71 mg/L**
Method	:	10 fishes per concentration and control, 10 fish per aquarium. The fish were ~26 mm in length, 0.15 g. The fish were not fed for 24 hours prior to exposure. The Glass aquaria were 20L capacity with 15 L dechlorinated tap water, hardness 176 mg CaCO3/L, temperature 23 ± 1°C. The aquaria were gently aerated during the test; the fish were provided fluorescent lighting 16 hours daily. Oxygen, pH, and temperature were measure daily. Due to the poor solubility of the test material in water, a stock solution of 4 g of the test substance and 40 mg alkylphenol-polyglycolether were mixed and made with 10 ml tetrahydrofuran. This solution was diluted appropriately. The nominal test concentrations were 10, 18, 32, 58, and 100 mg/L. Control = Water plus 132 mg tetrahydofuran and 1 mg alkylphenol-polyglycolether per liter water in the concentration used for the highest test concentration. Initially small parts of the test substance floated at the surface of all test concentrations and a slight deposit was observed after 72 hours of exposure in all test vessels. The analytically confirmed concentrations were 5.2, 11, 19, 46, and 71 mg/L. None of the fish died in any of the test vessels and there were no signs of altered swimming behavior, loss of equilibrium, respiratory effects, exopthalmus or pigmentation changes.
Year	:	1988
GLP	:	In spirit of GLP
Test substance	:	as prescribed by 1.1 - 1.4
Remark	:	96Hr LC50 is equivalent to highest concentration tested; thus value may be higher than reported.
Source	:	Report on the Test for Acute Toxicity of TK10030 to Zebra-Fish, Ciba-Geigy Ltd. Basle, Switzerland. December 2, 1988.
Reliability		This study is assigned a reliability code of 1b according to the

criteria established by Klimisch et al. (1997). It was conducted under OECD guidelines.

4.2 ACUTE TOXICITY TO AQUATIC INVERTEBRATES

Type	:	OECD Guideline 202
Species	:	Daphnia Magna Straus 1820
Exposure period	:	48 hour(s)
Unit	:	mg/l
Analytical monitoring	:	yes
LC50	:	**10 mg/L**
Method	:	20 daphnia per concentration and control, 4 replicates of 5 daphnia each. The daphnia were not fed during the test. The daphnia were obtained from in-house cultures at Ciba-Geigy Ltd., Basle, Switzerland. The water was reconstituted water prepared in a 1000 ml beaker; total hardness was 240 mg CaCO3/L. The water was aerated with clean air for at least 24 hrs before use. The daphnia were placed in 100 ml solution per beaker, covered with watch glasses. The temperature was maintained at 20 ± 1°C, 16 hours fluorescent lighting daily. Oxygen, pH, and temperature were checked at the start of the test. Due to the poor solubility of the test material in water, a stock solution of 2.5 g of the test substance and 40 mg alkylphenol-polyglycolether were mixed and made with 10 ml tetrahydrofuran. This solution was diluted to 100 mg/l with water. Control = Water plus 82.7 mg tetrahydofuran and 0.5 mg alkylphenol-polyglycolether per liter water in the concentration used for the highest test concentration. Nominal test concentrations were 3.2, 5.8, 10, 18, and 32 mg/L. Test material was added to the water prior to transfer in of the daphnia. A slight deposit was observed at all concentrations. The EC0 was determined to be <3.2 mg/L and the EC100 was determined to be 18 mg/L.
Year	:	1988
GLP	:	In spirit of GLP
Test substance	:	as prescribed by 1.1 - 1.4
Remark	:	None
Source	:	Report on the Test for Acute Toxicity of TK10030 to Daphnia Magna, Ciba-Geigy Ltd. Basle, Switzerland. November 25, 1988.
Reliability		This study is assigned a reliability code of 1b according to the criteria established by Klimisch et al. (1997). It was conducted

under OECD guidelines.

4.3 TOXICITY TO AQUATIC PLANTS E.G. ALGAE

Species	:	Green Algae (Scenedesmus subspicatus)
Type	:	87/302/EEC Algae Growth Inhibition Test
Endpoint	:	biomass
Exposure period	:	72 hour(s)
Unit	:	mg/l
Analytical monitoring	:	Values based on nominal concentrations
EbC50	:	**33.9 mg/L**
NOEbC (0-72 h)	:	11.0mg/L
Method	:	100 ml Erlenmeyer flasks with 50 ml test solution per flask were used. The temperature was maintained at 24 ± 1°C. Lighting was continuous cold white fluorescent light, 133 uE/m2 sec ± 20 %. Test concentrations were nominal determined to be 1.23, 3.7, 11, 33, and 100 mg/L. 3.0 g test substance and 3.0 g vehicle (96% n,n-dimethylformamide and 4% alkyl-phenol-polyglycolether (ARKOPAL)) were mixed together for 24 hours. 1 g of this blend was mixed with 9 g water and then 2 ml of this blend was mixed and made up to 1000 ml with water, achieving a concentration of 100 mg/L. Water plus vehicle was used as the blank. Each test concentration was tested in 3 replicates, the blank control in 6. Calculated amounts of the stock solution to produce the desired test concentrations were given into the water and were homogeneously distributed. The algae were then transferred into the flasks. The test substance was homogeneously distributed in the test vessels at all test times and test concentrations. Cell densities were measured at 24, 48, and 72 hours exposure on a TOA cell counter. Temperature was continuously measured and maintained at 23 ± 1°C. pH was measured at 0h and 72h exposure. The EbC 50 (0-72 h) = 33.9 mg/L 95% CL 29.5-38.3 mg/L. The NOEbC (0-72 h) (5% level = 11.0 mg/L).
Year	:	1992
GLP	:	In spirit of GLP
Test substance	:	as prescribed by 1.1 - 1.4
Remark	:	Values based on nominal concentrations.
Source	:	Report on the Growth Inhibition Test of IRGANOX PS 800 to Green Algae (Scenedesmus subspicatus), Ciba-Geigy Ltd.

Reliability

Basle, Switzerland. September 16, 1992.
This study is assigned a reliability code of 1b according to the criteria established by Klimisch et al. (1997). It was conducted under OECD guidelines.

5.1.1 ACUTE ORAL TOXICITY

Type	:	LD50
Species	:	rat
Strain	:	no data
Sex	:	no data
Number of animals	:	
Vehicle	:	other: olive oil
Value	:	**> 2500 mg/kg bw**
Method	:	
Year	:	1947
GLP	:	no
Test substance	:	as prescribed by 1.1 - 1.4
Method	:	Groups of 5 or 10 rats were dosed orally with 2000 or 2500 mg/kg, respectively. Test material was dissolved in olive oil. Dosed animals were observed for 7 days after dosing. Dosed animals were observed for 7 days after dosing.
Result	:	There were no deaths observed at either dose level. LD50: >2500 mg/kg.
Source	:	Tullar, P.E. (1947). The pharmacology and toxicology of thiodipropionic acid and its dilauryl and distearyl esters. Final Report. The Kalusowski Memorial Research Laboratories, School of Pharmacy, The George Washington University, Washington, D.C. Unpublished data. FDA FOIA request #F88-8055. Document #001974-002031.
Reliability	:	This study is assigned a reliability code of 2e according to the criteria established by Klimisch *et al.* (1997). It was not conducted under GLP or OECD guidelines but generally meets scientific standards, is well documented and is accepted for assessment.

Type	:	LD50
Species	:	rat
Strain	:	no data
Sex	:	male
Number of animals	:	
Vehicle	:	physiol. saline
Method	:	
Year	:	1973
GLP	:	no
Test substance	:	as prescribed by 1.1 - 1.4
Method	:	A group of twelve male rats was dosed with 5000 mg/kg while groups of 10 male rats were dosed with 50 or 500 mg/kg. Animals were necropsies on day 6.
Result	:	All animals survived to the scheduled necropsy and appeared normal during the five day observation period. No gross

morphological changes were observed.

Source	:	Litton Bionetics, Inc. (1973). Mutagenic evaluation of compound FDA 71-40, dilauryl thiodipropionic acid. US Dept of Commerce. NTIS PB245452.
Reliability	:	This study is assigned a reliability code of 2e according to the criteria established by Klimisch *et al.* (1997). It was not conducted under GLP or OECD guidelines but generally meets scientific standards, is well documented and is accepted for assessment.
Type	:	LD50
Species	:	mouse
Strain	:	no data
Sex	:	no data
Number of animals	:	
Vehicle	:	other: olive oil
Value	:	> 2000 mg/kg bw
Method	:	
Year	:	1947
GLP	:	no
Test substance	:	as prescribed by 1.1 - 1.4
Method	:	Groups of 19, 10, 20 or 20 mice were dosed orally with 300, 500, 1000 or 2000 mg/kg, respectively. Test material was dissolved in olive oil. Animals were observed for one week after dosing with test material.
Result	:	There were 4, 0, 0, 1 deaths observed at 300, 500, 1000 and 2000 mg/kg, respectively. LD50: >2000 mg/kg. No further information was provided.
Source	:	Tullar, P.E. (1947). The pharmacology and toxicology of thiodipropionic acid and its dilauryl and distearyl esters. Final Report. The Kalusowski Memorial Research Laboratories, School of Pharmacy, The George Washington University, Washington, D.C. Unpublished data. FDA FOIA request #F88-8055. Document #001974-002031.
Reliability	:	This study is assigned a reliability code of 2e according to the criteria established by Klimisch *et al.* (1997). It was not conducted under GLP or OECD guidelines but generally meets scientific standards, is well documented and is accepted for assessment.

5.2.1 SKIN IRRITATION

Species	:	human
Concentration	:	
Exposure	:	Occlusive

Exposure time	:	
Number of animals	:	16
PDII	:	
Result	:	
EC classification	:	
Method	:	
Year	:	1975
GLP	:	no
Test substance	:	as prescribed by 1.1 - 1.4
Method	:	Test population of 16 healthy adult male darkly pigmented volunteers over the age of 21 received applications to the lower back. A 1-inch square of non-woven fabric (Webril) covered with occlusive adhesive tape (Blenderm) was applied daily. Test material was applied daily for 60 consecutive days. The test site was examined weekly by the investigator. This was a double blind study in which samples were applied by code. Other antioxidants were also tested for comparison purposes. Each subject received four of the test compounds, which were assigned to the individuals on a random basis. The test sites were medicated on a random basis.
Result	:	There was no evidence of depigmentation in any subject when examined at the weekly intervals throughout the study or at two 1-month intervals thereafter. The authors mentioned that there was some evidence of irritation at some of the test sites and the control sties. They did not indicate that this was an exposure-related effect.
Source	:	Maibach, H.I., Gellin, G. and Ring, M. (1975). Is the antioxidant butylated hydroxytoluene a depigmenting agent in man? Contact Dermatitis 1:295-296.
Reliability	:	This study is assigned a reliability code of 2e according to the criteria established by Klimisch *et al.* (1997). It was not conducted under GLP guidelines but generally meets scientific standards, is well documented and is accepted for assessment.

5.2.2 EYE IRRITATION

Species	:	rabbit
Concentration	:	
Dose	:	
Exposure Time	:	
Comment	:	
Number of animals	:	2
Result	:	
EC classification	:	
Method	:	
Year	:	1947
GLP	:	no

Test substance	:	as prescribed by 1.1 - 1.4
Method	:	One drop of a solution containing 0.8 mg/ml was placed into the right conjunctival sacs of two rabbits.
Result	:	No signs of irritation were observed at 24 or 48 hours.
Source	:	Tullar, P.E. (1947). The pharmacology and toxicology of thiodipropionic acid and its dilauryl and distearyl esters. Final Report. The Kalusowski Memorial Research Laboratories, School of Pharmacy, The George Washington University, Washington, D.C. Unpublished data. FDA FOIA request #F88-8055. Document #001974-002031.
Reliability	:	This study is assigned a reliability code of 3b according to the criteria established by Klimisch *et al.* (1997). Test material too weak.
Species	:	rabbit
Concentration	:	
Dose	:	500 other: mg
Exposure Time	:	24 hour(s)
Comment	:	
Number of animals	:	
Result	:	
EC classification	:	
Method	:	
Year	:	1972
GLP	:	no
Test substance	:	as prescribed by 1.1 - 1.4
Method	:	Instillation of 500 mg neat material into rabbits eye for 24 hours.
Result	:	Mild irritation observed in rabbit eyes.
Source	:	Marhold, J. (1972). Sbornik Vysledku Toxikologickeho Vysetreni Latek A Pripravku, p. 174 Cited in NIOSH RTECS 98-3 (August 1998).
Reliability	:	This study is assigned a reliability code of 2e according to the criteria established by Klimisch *et al.* (1997). It was not conducted under GLP guidelines but generally meets scientific standards, is well documented and is accepted for assessment.

5.3 SENSITIZATION

Type	:	
Species	:	guinea pig
Number of animals	:	
Vehicle	:	
Result	:	
Classification	:	
Method	:	
Year	:	1960

GLP	:	no
Test substance	:	as prescribed by 1.1 - 1.4
Method	:	No further information supplied.
Result	:	Negative in a guinea pig skin sensitization study.
Source	:	Bar, F. and Griepentrog, F. (1960). Medizin Ernahr 1:100 cited in BIBRA (1989). Didodecyl thiodipropionate.
Reliability	:	This study is assigned a reliability code of 3a according to the criteria established by Klimisch *et al.* (1997). Documentation is insufficient for assessment.
Type	:	
Species	:	human
Number of animals	:	
Vehicle	:	
Classification	:	
Method	:	
Year	:	1975
GLP	:	no
Test substance	:	as prescribed by 1.1 - 1.4
Method	:	Test population consisted of 16 healthy adult male darkly pigmented volunteers over the age of 21 received applications to the lower back. A 1-inch square of non-woven fabric (Webril) covered with occlusive adhesive tape (Blenderm) was applied daily. Test material was applied daily for 60 consecutive days. The test site was examined weekly by the investigator. This was a double blind study in which samples were applied by code. Three other antioxidants, butylated hydroxytoluene (BHT), 4-hydroxymethyl-2,6-di-tert-butylphenol and 4,4'-methylinebis (2,6-di-tert-butylphenol), were also tested for comparison purposes. One antioxidant, BHT, was tested at 3 concentrations. Each subject received four of the test compounds, which were assigned to the individuals on a random basis. The test sites were medicated on a random basis. Since the test material was applied 60 times, the length was sufficiently long enough to detect dermal sensitizer.
Result	:	There was no evidence of dermal sensitization.
Source	:	Maibach, H.I., Gellin, G. and Ring, M. (1975). Is the antioxidant butylated hydroxytoluene a depigmenting agent in man? Contact Dermatitis 1:295-296.
Reliability	:	This study is assigned a reliability code of 2e according to the criteria established by Klimisch *et al.* (1997). It was not conducted under GLP guidelines but generally meets scientific standards, is well documented and is accepted for assessment.

5.4 REPEATED DOSE TOXICITY

Species	:	rat
Sex	:	10 per sex per group (weeks 1-13); 5 per sex for the control and high dose treatment-free extension groups
Strain	:	Sprague-Dawley; 6 weeks of age at initiation of study.
Route of admin.	:	oral gavage
Body Weight Range	:	Males: 162-193 g; Females: 142-180g (at study initiation)
Exposure period	:	13 weeks with a 4 week treatment-free period.
Frequency of treatment	:	daily
Post obs. period	:	yes, 4 weeks
Doses	:	125, 350, and 1000 mg/kg/day
Control group	:	yes
Method	:	13 Week Oral (gavage) Toxicity Study in the Rat followed by a 4 Week Treatment-free Period.
Summary Result	:	**NOAEL = 350 mg/kg/day; NOEL = 125 mg/kg/day**
Year	:	1993
GLP	:	Yes
Test substance	:	as prescribed by 1.1 - 1.4
Method	:	Groups of 10 rats per sex per group were given doses of 0, 125, 350, or 1000 mg/kg/day by gavage, using a metal cannula for approximately 13 weeks. Dosing solutions were made daily and concentrations were analytically confirmed at weeks 1, 4, 8, and 13. The gavage vehicle was 1% carboxymethyl cellulose in water. Animals were housed in groups of 5 of the same sex and dose group per cage. The animal room was maintained at 19-25C, 35-75% relative humidity, and a 12 hour light/12 hour dark lighting cycle. Rats were fed ad lib, but fasted ~16 hours prior to blood sampling, during the collection of urine, and before necropsy. Water was also provided ad lib, but withheld during urine collection. All animals were observed twice daily for morbidity and mortality. Clinical observations were done daily, with full clinical evaluations done weekly. Body weights and food consumption were recorded weekly. Opthalmoscopy was performed on all animals pretest and at week 13 in the control and high dose animals. Clinical pathology was performed on 10 animals/sex in control and high dose groups after week 4, 10 animals/sex in all groups after week 13, and in all recovery animals after week 17. Parameters included hematology (except on treatment-free period animals), blood clinical chemistry, and urinalysis. All animals were submitted to full necropsy. Organ weights were taken at necropsy. Histopathology was performed on all selected organs/tissues for all animals in the control and high dose groups, the liver, kidneys and lungs for all animals in all groups, and the heart from animals in groups

2 and 3 and in all recovery group animals. The hearts from all animals was examined after PTAH staining.

Remark : **Organs examined histologically also included the epidiymides, mammary glands, ovaries, prostate, seminal vesicles, testes, uterus (horn + cervix). This is suggestive of no adverse effects on reproduction.**

Result : There were no unscheduled deaths and no treatment related clinical signs. There were no treatment related differences in body weight gain and food consumption was unaffected by treatment. There were no treatment related eye lesions. None of the hematological parameters were considered to represent an adverse effect of treatment. None of the clinical chemistry parameters other than a reversible elevation in serum cholesterol in the high dose females and a reversible elevation of alanine and aspartate aminotransferase activities in all high dose animals were related to an effect of treatment. Urine parameters were unaffected other than being slightly more acidic in the high dose animals as compared to the controls. This was reversible after the 4 week treatment-free period. The minor differences in the weight of the major organs were considered of no toxicological significance in the absence of microscopic lesions. Macroscopic changes were considered to either be agonal or incidental in origin or unrelated to treatment. Treatment-related microscopic lesions were seen in the heart of high dose animals. The lesion was described as small foci of degenerated or necrotic fibers associated with minimal to moderate mononuclear cell infiltration. This association suggested early or ongoing myocarditis. These lesions were not present in animals previously treated at the high dose level but allowed a 4 week period without treatment. There were no other treatment related microscopic lesions.

In conclusion, the oral (gavage) administration of DLTDP to the rat for 13 weeks at a dose level of 1000 mg/kg/day was associated with a minor increase in serum cholesterol concentrations in females, increased serum ALAT and ASAT activities and decreased urinary pH in both sexes. Microscopic findings in the heart of these animals suggested an ongoing myocarditis. The heart was therefore identified as the target organ. All these changes were reversible after 4 weeks without treatment. At a dose level of 350 mg/kg/day there was no evidence for any treatment related microscopic change in the heart. Females at this dose exhibited a very small, but not statistically significant, increase in Hb concentrations. These individual values fell with in the normal background range and are considered unlikely to be a direct toxic effect of the test material. Clinical chemistry results indicated calcium concentrations of the males were slightly

elevated compared with controls. However, the differences were small, not statistically significant and generally well within the normal background range. No other differences to indicate an adverse effect of the test article were noted. This dose level is therefore considered to be the no observed adverse effect level for DLTDP in the rat. There were no changes considered to represent an effect of the test article at 125 mg/kg/day and therefore this dose level is considered to be the no observed effect level for DLTDP in the rat.

Source : 13 Week Oral (gavage) Toxicity Study in the Rat followed by a 4 Week Treatment-free Period. Ciba-Geigy Ltd. Basel Switzerland. December 14, 1993.

Reliability : This study is assigned a reliability code of 1b according to the criteria established by Klimisch *et al.* (1997). It was conducted under GLP guidelines but uses a non-specified protocol method that generally meets scientific standards, is well documented and is acceptable for assessment.

Species : rat
Sex : male
Strain : no data
Route of admin. : oral feed
Exposure period : 2 years
Frequency of treatment : daily
Post obs. period :
Doses : 0.5 and 3%
Control group : yes
Method :
Year : 1947
GLP : no
Test substance : as prescribed by 1.1 - 1.4
Method : Initially, groups of 10 male albino rats were fed 0, 0.5 or 3.0% dilauryl thiodipropionate in the diet for approximately 6 months. The control group consisted of 11 males. Weekly records were kept of average body weights, feed consumption, moralities, general appearance and gross pathology over a period of 292 days. Subsequently, decision was made to extend exposure period to 2 years. No additional information was provided.

Remark : Not reliable due to disease, small number of animals and lack of pathology.

Result : Two controls and three males from the 3.0% dose group died during the first 6 months. Approximately 4 months into the study, some animals ingesting similar materials succumbed to Salmonellosis (described by authors as possible 'paratyphoid' infection). At the end of the two years, 9 of 11 controls, 9 of 10 from the 0.5% group and 10 of 10 from the 3.0% group had

died. Mortality in the controls occurred during the final months of the experiment, in contrast, mortality in the treated groups occurred from 6 months to a year earlier. Ingestion of dilauryl thiodipropionate did not seriously affect weight development or general appearance.

Source : Tullar, P.E. (1947). The pharmacology and toxicology of thiodipropionic acid and its dilauryl and distearyl esters. Final Report. The Kalusowski Memorial Research Laboratories, School of Pharmacy, The George Washington University, Washington, D.C. Unpublished data. FDA FOIA request #F88-8055. Document #001974-002031.

Reliability : This study is assigned a reliability code of 3a according to the criteria established by Klimisch *et al.* (1997). Documentation is insufficient for assessment.

Species : dog
Sex :
Strain :
Route of admin. :
Exposure period :
Frequency of treatment :
Post obs. period :
Doses :
Control group :
Method :
Year : 1947
GLP : no
Test substance : as prescribed by 1.1 - 1.4
Method : Groups consisting of one dog were fed a 10:1 mixture of dilauryl thiodipropionate and thiodipropionic acid at 0.1, 1.0 or 3.0% in the diet for 100 days. Material was heated to 190C for 30 minutes. This corresponded to approximately 25, 250 or 750 mg mixture/kg body weight/day in the diet. Excess food was given once a day, allowing ample time for maximum voluntary consumption. Daily records of food consumption were maintained, and the weights of the dogs were recorded weekly. Urinalysis and blood counts were repeated after a period of one month and again at the termination of the experiment.
At the termination of the study, the dogs were sacrificed and histological sections were made of the kidneys, livers, spleens, and pancreas.

Result : The dog receiving 1% in the diet became sick on the eighth day died on the tenth day of the experiment, apparently from distemper. "No untoward effects" were observed on the survivors and no further information was provided

Source : Tullar, P.E. (1947). The pharmacology and toxicology of

thiodipropionic acid and its dilauryl and distearyl esters. Final Report. The Kalusowski Memorial Research Laboratories, School of Pharmacy, The George Washington University, Washington, D.C. Unpublished data. FDA FOIA request #F88-8055. Document #001974-002031.

Reliability : This study is assigned a reliability code of 3a according to the criteria established by Klimisch *et al.* (1997). Documentation is insufficient for assessment.

5.5 GENETIC TOXICITY 'IN VITRO'

Type : **Ames test**
System of testing :
Concentration : 33.3, 100, 333, 1000, 2500, 3333, 5000, 6667, and 10,000 ug/plate and 3.3 and 10 ug/plate for strain TA100
Cytotoxic conc. : No toxicity was observed at 10,000 ug/plate with and without metabolic activation.
Metabolic activation : with and without
Result : **negative**
Method : other: essentially follows OECD 471
Year : 1979
GLP : no
Test substance : as prescribed by 1.1 - 1.4
Method : Tested with and without metabolic activation using Salmonella typhimurium strains TA1535, TA1537, TA1538, TA98 and TA100 and Escherichia coli strain WP2. Liver S-9 fraction from Aroclor 1254 pretreated male Sprague-Dawley rats with NADPH generating system was used for metabolic activation. The experiment was repeated approximately 6 weeks later.

Sodium azide was used as the positive control without metabolic activation while 2-anthramine was used as the positive control with metabolic activation.

Result : A precipitate was observed at the two highest doses tested. These plates were hand-counted. There was no evidence that it was mutagenic in the assays performed.
Flag : Critical study for SIDS endpoint
Source : SRI International (1979). Microbial mutagenesis testing of substances; compound report: F76-049, dilauryl thiodipropionate. NTIS report PB89169031.
Reliability : This study is assigned a reliability code of 1b according to the criteria established by Klimisch *et al.* (1997). It was not conducted under GLP guidelines but uses methods that generally meet scientific standards, is well documented and is acceptable for assessment.

Type : Cytogenetic assay

System of testing	:	
Concentration	:	5.0, 50 or 500 ug/ml
Cytotoxic conc.	:	
Metabolic activation	:	
Result	:	negative
Method	:	other: In vitro cytogenetics study using human embryonic lung cultures, WI-38
Year	:	1973
GLP	:	no
Test substance	:	other TS: dilauryl thiodipropionic acid
Method	:	Human embryonic lung cultures were suspended in tissue culture medium (minimal essential medium plus 1% glutamine, 200 units/ml penicillin and 200 ug/ml of streptomycin and 15% fetal calf serum) for 24 hours. Dose levels of 5.0, 50 or 500 ug/ml were tested. Cells were incubated at 37C and examined twice daily. When an adequate number of mitoses were present, usually 24-48 hours after planting, cells were harvested by centrifuging and fixed in absolute methanol:glacial acetic acid (3:1) for 30 minutes. Specimens were centrifuged, decanted and suspended in acetic acid-orcein stain (2.0%). A drop was placed on a slide and 100 cells were counted. The percentage of anaphase cells was determined.
Result	:	There were no significant aberrations in the anaphase chromosomes of human tissue culture cells at dose levels as high as 500 ug/ml.
Source	:	Litton Bionetics, Inc (1973) Mutagenic evaluation of compound FDA 71-40, dilauryl thiodipropionic acid. NTIS PB245452.
Reliability	:	This study is assigned a reliability code of 2e according to the criteria established by Klimisch *et al.* (1997). It was not conducted under GLP or OECD guidelines but generally meets scientific standards, is well documented and is acceptable for assessment.

Type	:	other: in vitro host mediated assay
System of testing	:	
Concentration	:	
Cytotoxic conc.	:	
Metabolic activation	:	
Result	:	negative
Method	:	
Year	:	1973
GLP	:	no
Test substance	:	other TS: dilauryl thiodipropionic acid
Method	:	Two histidine auxotrophs, his G-46 and TA-1530 of Salmonella

typhimurium and a diploid strain D-3 of Saccharomyces cerevisiae, were used.

Dimethyl nitrosamine was used as a positive control for Salmonella and ethyl methane sulfonate (EMS) was used for Saccharomyces.

Source : Litton Bionetics, Inc (1973) Mutagenic evaluation of compound FDA 71-40, dilauryl thiodipropionic acid. NTIS PB245452.

Ames (1971). The detection of chemical mutagens with enteric bacteria. Chemical Mutagens: Principles and methods for their detection. Vol 1 Chapter 9:267-282.

Reliability : This study is assigned a reliability code of 3c according to the criteria established by Klimisch *et al.* (1997). Unsuitable test system.

5.6 GENETIC TOXICITY 'IN VIVO'

Type	:	Dominant lethal assay
Species	:	rat
Sex	:	
Strain	:	no data
Route of admin.	:	gavage
Exposure period	:	an acute study and subacute study (dosed once/day for 5 days)
Doses	:	50, 500 or 5000 mg/kg
Result	:	negative
Method	:	other: essentially follows OECD 478
Year	:	1973
GLP	:	no
Test substance	:	other TS: dilauryl thiodipropionic acid
Method	:	Male and female rats from a closed colony were used. Animals were 10-12 weeks old at the time of use. Ten male rats were assigned to each of 5 groups; 3 dose levels of dilauryl thiodipropionic acid, 50, 500 or 5000 mg/kg, a positive control, triethylene melamine, and a negative control group. The positive control was administered intraperitoneally at a dose level of 0.3 mg/kg. Administration of the test compound was orally by intubation in both the acute study and in the subacute study (dosed once/day for 5 days). Following treatment, the males were sequentially mated to 2 females/week for 8 weeks (7 weeks in the subacute study). Two virgin female rats were housed with a male for 5 days (Monday through Friday). These two females were removed and housed in a cage until sacrificed. The males were left alone for two days and two new females were housed with a

male for the next 5 days (Monday through Friday). Females were killed using carbon dioxide at 14 days after separation from the male and at necropsy the uterus was examined for early deaths, late fetal deaths and total implantations.

Result : There was no clear pattern of either increases or decreases between the control and test groups in any of the parameters studied. Thus, dilauryl thiodipropionic acid was considered to be non-mutagenic in rats in the dominant lethal assay when using the dosages employed in this study.

Flag : Critical study for SIDS endpoint

Source : Litton Bionetics, Inc (1973) Mutagenic evaluation of compound FDA 71-40, dilauryl thiodipropionic acid. NTIS PB245452.

Reliability : This study is assigned a reliability code of 1b according to the criteria established by Klimisch *et al.* (1997). It was not conducted under GLP guidelines but uses methods that generally meet scientific standards, is well documented and is acceptable for assessment.

Type : **Micronucleus assay**

Species : rat

Sex : male

Strain : no data

Route of admin. : gavage

Exposure period :

Doses :

Result : **negative**

Method : other: essentially follows OECD 474 in vivo mammalian bone marrow micronucleus test

Year : 1973

GLP : no

Test substance : other TS: dilauryl thiodipropionic acid

Method : In the acute phase, groups of 5 male albino rats were sacrificed 6, 24 or 48 hours after dosing by oral gavage with 50, 500 or 5000 mg/kg dilauryl thiodipropionic acid. The negative control group of 9 rats received saline. The positive control group of 5 male rats received 0.3 mg/kg triethylene melamine and was sacrificed 48 hours after dosing. Two hours prior to each sacrifice, each animal received 4 mg/kg of colcemid intraperitoneally. Animals were sacrificed with carbon dioxide. The epiphysis of one femur was removed and the marrow aspirated into 5 ml of Hanks' balanced salt solution. The specimens were centrifuges at 1500 rpm for 5 minutes, decanted and 2 ml of hypotonic 0.5% KCl solution was aged with gentle agitation to resuspend the cells. The specimens were then placed in a 37C water bath for 20 minutes in order to swell the cells. Following centrifugation for 5 minutes at 1500 ppm, the supernatant was decanted and 2

ml of fixative (3:1 absolute methanol:glacial acetic acid) was added. The cells were resuspended in the fixative with gentile agitation, capped and maintained at 4C for 30 minutes. The specimens were again centrifuged, decanted, 2 ml of prepared fixative was added, and the cells were resuspended and maintained at 4C overnight. Cells were placed on a slide and stained with a 5% Giemsa solution for 20 minutes, rinsed in acetone, 1:1 acetone:xylene, and placed in fresh xylene for 30 minutes. Fifty metaphase spreads were scored per animal. Mitotic indices were obtained by counting at least 500 cells and the ratio of the number of cells in mitosis/the number of cells observed was expressed as the mitotic index.

Result : The compound produced no detectable significant aberration of the bone marrow metaphase chromosomes of rats when administered orally at the dosage levels employed in this study following acute or short term exposure.

Mitotic indices were normal.

Flag : Critical study for SIDS endpoint

Source : Litton Bionetics, Inc (1973) Mutagenic evaluation of compound FDA 71-40, dilauryl thiodipropionic acid. NTIS PB245452.

Reliability : This study is assigned a reliability code of 1b according to the criteria established by Klimisch *et al.* (1997). It was not conducted under GLP guidelines but uses methods that generally meet scientific standards, is well documented and is acceptable for assessment.

Type : other: host mediated assay

Species : mouse

Sex : male

Strain : ICR

Route of admin. : gavage

Exposure period : 3 hours

Doses : 50, 500 or 5000 mg/kg

Result : ambiguous

Method :

Year : 1973

GLP : no

Test substance : other TS: dilauryl thiodipropionic acid

Method : Groups of 10 ICR random-bred male mice were used in the acute and subacute studies. Dilauryl thiodipropionic acid was administered orally by intubation at doses of 50, 500 or 5000 mg/kg. The positive control group received either 100 mg/kg dimethylnitrosamine in the case of Salmonella or 350 mg/kg ethylmethane sulfonate in the case of Saccharomyces. All animals received 2 ml of the indicator organism intraperitoneally. Each ml contained 3.0 x 10 8 cells of

Salmonella (his G-46 and TA-1530) and 5.0 x 108 cells of Saccharomyces (D-3). Three hours later each animal was sacrificed and 2 ml sterile saline introduced intraperitoneally. As much fluid as possible was then aseptically removed from the peritoneal cavity. Tenfold serial dilutions were made of each peritoneal exudate yielding a concentration series from 100 through 10-7. For enumeration of total bacterial counts, the 10-6 and 10-7 dilutions were plated on tryptone yeast extract agar. In plating for the total mutant counts on minimal agar, the 100 dilution was used. The plating procedure was identical to that followed for the tryptone yeast extract agar plates. All plates were incubated at 37C, tryptone yeast extract plates for 18 hours and minimal agar plates for 40 hours. For yeast mitotic recombination, ten-fold serial dilutions were made of each sample yielding a series from 100 to 10-5. Samples of 0.1 ml of the 10-5, 10-4, and 10-3 dilutions were removed and plated on complete medium (10 plates each). All plates were incubated at 30C for 40 hours. The 10-5 dilutions were used to determine total populations and 10-4 and 10-3 plates were examined after an additional 40 hours at 4C for mutations. Mutations were seen as red colonies or as red sectors on a normally white yeast colony.

Result : Dilauryl thiodipropionic acid produced no significant reversion or recombinant increases in Salmonella strain TA-1530 or Saccharomyces strain D-3, respectively. The results from tests using Salmonella strain G-46 indicated that this compound induced reversion in both the acute and subacute trials. A slight dose response was observed in the acute trials (0.54, 2.11, 4.51 and 5.36 in the control, 50, 500 and 5000 mg/kg groups, respectively) but not in the subacute trials (0.62, 5.62, 6.03 and 6.33 in the control, 50, 500 and 5000 mg/kg groups respectively). Repeat tests of the acute trials indicated the compound induced reversion, although the results were not dose dependent (5.42, 6.82 and 5.99 in the 50, 500 and 5000 mg/kg group, respectively).

Source : Litton Bionetics, Inc (1973) Mutagenic evaluation of compound FDA 71-40, dilauryl thiodipropionic acid. NTIS PB245452.

Reliability : This study is assigned a reliability code of 2e according to the criteria established by Klimisch *et al.* (1997). It was not conducted under GLP or OECD guidelines but uses methods that generally meet scientific standards, is well documented and is acceptable for assessment.

5.7 CARCINOGENITY

Species : rat

Sex	:	no data
Strain	:	no data
Route of admin.	:	oral feed
Exposure period	:	two years
Frequency of treatment	:	continuous
Post. obs. period	:	
Doses	:	0.5, 1.0 and 3.0%
Result	:	
Control group	:	yes
Method	:	
Year	:	1951
GLP	:	no
Test substance	:	as prescribed by 1.1 - 1.4
Method	:	Groups of 20 male rats/dose level were fed 0.5, 1.0 or 3.0% in the diet for two years. Feed consumption was obtained weekly and body weights were obtained at appropriate intervals. Gross and histopathologic examinations were conducted. No further details provided.
Remark	:	Not reliable due to small number of animals and lack of pathology detail
Result	:	Body weights were decreased slightly in rats receiving 1.0 and 3.0% in the diet for the first 6 months of a 2 year study. Body weights were unaffected in rats receiving 0.5% in the diet over the same time period. Mortality was unaffected during the first 9 months of the study. Mortality was higher in high dose group with 10, 7 and 16 animals ingesting 0.5, 1.0 or 3.0%, respectively dead at the end of the study. There were no significant differences in average body weights or histopathologic changes in the rats exposed to 3.0% dilauryl thiodipropionate in the diet for up to 2 years.
Source	:	Lehman, A.J. et al., (1951). The pharmacological evaluation of antioxidants. Advances in Food Research. 3:197-208.
Reliability	:	This study is assigned a reliability code of 2e according to the criteria established by Klimisch *et al.* (1997). It was not conducted under GLP or OECD guidelines but uses methods that generally meet scientific standards, is well documented and is acceptable for assessment.

5.8 TOXICITY TO REPRODUCTION

Species	:	rat
Sex	:	10 per sex per group (weeks 1-13); 5 per sex for the control and high dose treatment-free extension groups
Strain	:	Sprague-Dawley; 6 weeks of age at initiation of study.
Route of admin.	:	oral gavage

5. Toxicity

Id 123-28-4
Date 01/14/03

Body Weight Range	:	Males: 162-193 g; Females: 142-180g (at study initiation)
Exposure period	:	13 weeks with a 4 week treatment-free period.
Frequency of treatment	:	daily
Post obs. period	:	yes, 4 weeks
Doses	:	125, 350, and 1000 mg/kg/day
Control group	:	yes
Method	:	13 Week Oral (gavage) Toxicity Study in the Rat followed by a 4 Week Treatment-free Period.
Summary Result	:	**NOAEL = 350 mg/kg/day; NOEL = 125 mg/kg/day**
Year	:	1993
GLP	:	Yes
Test substance	:	as prescribed by 1.1 - 1.4
Method	:	Groups of 10 rats per sex per group were given doses of 0, 125, 350, or 1000 mg/kg/day by gavage, using a metal cannula for approximately 13 weeks. The gavage vehicle was 1% carboxymethyl cellulose in water. Dosing solutions were made daily and concentrations were analytically confirmed at weeks 1, 4, 8, and 13. Animals were housed in groups of 5 of the same sex and dose group per cage. The animal room was maintained at 19-25C, 35-75% relative humidity, and a 12 hour light/12 hour dark lighting cycle. Rats were fed ad lib, but fasted ~16 hours prior to blood sampling, during the collection of urine, and before necropsy. Water was also provided ad lib, but withheld during urine collection. All animals were observed twice daily for morbidity and mortality. Clinical observations were done daily, with full clinical evaluations done weekly. Body weights and food consumption were recorded weekly. Opthalmoscopy was performed on all animals pretest and at week 13 in the control and high dose animals. Clinical pathology was performed on 10 animals/sex in control and high dose groups after week 4, 10 animals/sex in all groups after week 13, and in all recovery animals after week 17. Parameters included hematology (except on treatment-free period animals), blood clinical chemistry, and urinalysis. All animals were submitted to full necropsy. Organ weights were taken at necropsy. Histopathology was performed on all selected organs/tissues for all animals in the control and high dose groups, the liver, kidneys and lungs for all animals in all groups, and the heart from animals in groups 2 and 3 and in all recovery group animals. The hearts from all animals was examined after PTAH staining.
Remark	:	**Organs examined histologically also included the epidiymides, mammary glands, ovaries, prostate, seminal vesicles, testes, uterus (horn + cervix). This is suggestive of no adverse effects on reproduction.**
Result	:	There were no unscheduled deaths and no treatment related

clinical signs. There were no treatment related differences in body weight gain and food consumption was unaffected by treatment. There were no treatment related eye lesions. None of the hematological parameters were considered to represent an adverse effect of treatment. None of the clinical chemistry parameters other than a reversible elevation in serum cholesterol in the high dose females and a reversible elevation of alanine and aspartate aminotransferase activities in all high dose animals were related to an effect of treatment. Urine parameters were unaffected other than being slightly more acidic in the high dose animals as compared to the controls. This was reversible after the 4 week treatment-free period. The minor differences in the weight of the major organs were considered of no toxicological significance in the absence of microscopic lesions. Macroscopic changes were considered to either be agonal or incidental in origin or unrelated to treatment. The treatment related microscopic lesions were seen in the heart of high dose animals. The lesion was described as small foci of degenerated or necrotic fibers associated with minimal to moderate mononuclear cell infiltration. This association suggested early or ongoing myocarditis. These lesions were not present in animals previously treated at the high dose level but allowed a 4 week period without treatment. There were no other treatment related microscopic lesions.

In conclusion, the oral (gavage) administration of DLTDP to the rat for 13 weeks at a dose level of 1000 mg/kg/day was associated with a minor increase in serum cholesterol concentrations in females, increased serum ALAT and ASAT activities and decreased urinary pH in both sexes. Microscopic findings in the heart of these animals suggested on ongoing myocarditis. The heart was therefore identified as the target organ. All these changes were reversible after 4 weeks without treatment. At a dose level of 350 mg/kg/day there was no evidence for any microscopic change in the heart and not other differences to indicate an adverse effect of the test article. This dose level is therefore considered to be the no observed adverse effect level for DLTDP in the rat. There were no changes considered to represent an effect of the test article at 125 mg/kg/day and therefore this dose level is considered to be the no observed effect level for DLTDP in the rat.

Source : 13 Week Oral (gavage) Toxicity Study in the Rat followed by a 4 Week Treatment-free Period. Ciba-Geigy Ltd. Basel Switzerland. December 14, 1993.

Reliability	:	This study is assigned a reliability code of 1b according to the criteria established by Klimisch *et al.* (1997). It was conducted under GLP guidelines but uses a non-specified protocol method that generally meets scientific standards, is well documented and is acceptable for assessment.

5.9 DEVELOPMENTAL TOXICITY/TERATOGENICITY

Species	:	**rat**
Sex	:	female
Strain	:	Wistar
Route of admin.	:	gavage
Exposure period	:	Days 6-15 of gestation
Frequency of treatment	:	
Duration of test	:	
Doses	:	16, 74, 350 or 1600 mg/kg in corn oil
Control group	:	yes
NOAEL Maternalt.	:	**= 1600 mg/kg bw**
NOAEL Teratogen	:	**= 1600 mg/kg bw**
Method	:	other: essentially follows OECD 414
Year	:	1972
GLP	:	no
Test substance	:	other TS: dilauryl thiodipropionic acid. Purity not stated.
Method	:	A positive control group received 250 mg/kg aspirin. Frequency of treatment for positive control group not stated. The number of pregnant rats at the end of the study ranged from 19-21/dose level. Feed and water were available ad libitum. The rats were observed daily for general appearance and behavior, with emphasis on feed consumption and weight. Weights were obtained on days 0, 6, 11, 15 and 20 of gestation. On day 20 of gestation caesarian sections were performed and the numbers of implantation and resorption sites as well as the numbers of live and dead fetuses were recorded. The urogenital tract of each dam was examined for any abnormality, all fetuses were examined for any gross external abnormalities, and all live pups were weighed. Visceral examinations were performed on one-third of the fetuses of each litter, and the remaining two-thirds were examined for skeletal defects.
Result	:	No adverse effects with respect to number of implantations and maternal or fetal death were noted after oral administration to rats of up to 1600 mg/kg dilauryl thiodipropionic acid on days 6-15 of gestation. There were no significant differences in numbers of abnormalities of the soft or skeletal tissues between the treated and sham control fetuses.

5. Toxicity

Id 123-28-4
Date 01/14/03

Flag	:	Critical study for SIDS endpoint
Source	:	Food and Drug Research Labs, Inc. (FDRL). (Dec. 29, 1972). Teratologic evaluation of FDA 71-40 (Dilauryl thiodipropionic acid) in mice, rats, and hamsters. Springfield, VA: U.S. Department of Commerce, National Technical Information Service (NTIS). NTIS publication #PB221 77.
Reliability	:	This study is assigned a reliability code of 1b according to the criteria established by Klimisch *et al.* (1997). It was not conducted under GLP guidelines but uses methods that generally meet scientific standards, is well documented and is acceptable for assessment.
Species	:	**mouse**
Sex	:	female
Strain	:	CD-1
Route of admin.	:	gavage
Exposure period	:	days 6-15 of gestation
Frequency of treatment	:	daily
Duration of test	:	
Doses	:	16, 74, 350 and 1600 mg/kg in corn oil
Control group	:	yes
NOAEL Maternalt.	:	**= 1600 mg/kg bw**
NOAEL Teratogen	:	**= 1600 mg/kg bw**
Method	:	other: essentially follows OECD 414
Year	:	1972
GLP	:	no
Test substance	:	other TS: dilauryl thiodipropionic acid. Purity not stated.
Method	:	A positive control group received 150 mg/kg aspirin. Frequency of treatment for the positive control not stated. The number of pregnant mice at the end of the study ranged from 20-22/dose level. Feed and water were available ad libitum. The mice were observed daily for general appearance and behavior, with emphasis on feed consumption and weight. Weights were obtained on days 0, 6, 11, 15 and 17 of gestation. On day 17 of gestation caesarian sections were performed and the numbers of implantation and resorption sites as well as the numbers of live and dead fetuses were recorded. The urogenital tract of each dam was examined for any abnormality, all fetuses were examined for any gross external abnormalities, and all live pups were weighed. Visceral examinations were performed on one-third of the fetuses of each litter, and the remaining two-thirds were examined for skeletal defects.
Result	:	No adverse effects were found with respect to implantations and maternal and fetal survival after oral administration to mice of up to 1600 mg/kg TDPA on days 6-15 of gestation. The number of abnormalities seen in the soft or skeletal

tissues of the treated fetuses was comparable to that seen in the sham control fetuses.

Source	:	Food and Drug Research Labs, Inc. (FDRL). (Dec. 29, 1972). Teratologic evaluation of FDA 71-40 (Dilauryl thiodipropionic acid) in mice, rats, and hamsters. Springfield, VA: U.S. Department of Commerce, National Technical Information Service (NTIS). NTIS publication #PB221 77.
Reliability	:	This study is assigned a reliability code of 1b according to the criteria established by Klimisch *et al.* (1997). It was not conducted under GLP guidelines but uses methods that generally meet scientific standards, is well documented and is acceptable for assessment.
Species	:	**rabbit**
Sex	:	female
Strain	:	Dutch
Route of admin.	:	gavage
Exposure period	:	days 6-18 of gestation
Frequency of treatment	:	daily
Duration of test	:	
Doses	:	2.5, 10, 45, 216, 1000 mg/kg in corn oil
Control group	:	yes
NOAEL Maternalt.	:	**= 1000 mg/kg bw**
NOAEL Teratogen	:	**= 1000 mg/kg bw**
Method	:	other: essentially follows OECD 414
Year	:	1973
GLP	:	no
Test substance	:	other TS: dilauryl thiodipropionic acid. Purity not stated.
Method	:	Groups of 15-29 artificially inseminated females/dose level resulted in 8-13 pregnant rabbits/dose level. On day 29, all does were subjected to c-section. The numbers of corpora lutea, implantation sites, resorption sites, and live and dead fetuses recorded. The body weights of the live pups were also recorded. The urogenital tract of each animal was examined in detail for normality. All fetuses underwent a detailed gross examination for the presence of external congenital abnormalities. The live fetuses of each litter were then placed in an incubator for 24 hours for the evaluation of neonatal survival. All surviving pups were sacrificed, and all pups examined for visceral abnormalities by dissection. All fetuses were then cleared in potassium hydroxide, stained with alizarin red S dye and examined for skeletal defects.
Result	:	Eight to thirteen pregnant dams survived to term. There was no clearly discernible effect on nidation or on maternal or fetal survival at doses as high as 1000 mg/kg. The number of abnormalities seen in either soft or skeletal tissues of the test groups did not differ from the number occurring spontaneously

		in the control
Flag	:	Critical study for SIDS endpoint
Source	:	FDA (1973). Teratologic evaluation of FDA 71-40 (dilauryl thiodipropionic acid) NTIS PB-223 824.
Reliability	:	This study is assigned a reliability code of 1b according to the criteria established by Klimisch *et al.* (1997). It was not conducted under GLP guidelines but uses methods that generally meet scientific standards, is well documented and is acceptable for assessment.
Species	:	**hamster**
Sex	:	female
Strain	:	other: golden
Route of admin.	:	gavage
Exposure period	:	Day 6-10 of gestation
Frequency of treatment	:	daily
Duration of test	:	
Doses	:	16, 74, 350 or 1600 mg/kg in corn oil
Control group	:	yes
NOAEL Maternalt.	:	**= 1600 mg/kg bw**
NOAEL Teratogen	:	**= 1600 mg/kg bw**
Method	:	other: essentially follows guideline 414
Year	:	1972
GLP	:	no
Test substance	:	other TS: dilauryl thiodipropionic acid. Purity not stated.
Method	:	The number of hamsters at the end of the study ranged from 20-23/dose level. Feed and water were available ad libitum. The hamsters were observed daily for general appearance and behavior, with emphasis on feed consumption and weight. Weights were obtained on days 0, 8, 10 and 14 of gestation. On day 14 of gestation caesarian sections were performed and the numbers of implantation and resorption sites as well as the numbers of live and dead fetuses were recorded. The urogenital tract of each dam was examined for any abnormality, all fetuses were examined for any gross external abnormalities, and all live pups were weighed. Visceral examinations were performed on one-third of the fetuses of each litter, and the remaining two-thirds were examined for skeletal defects.
Result	:	The numbers of implantations and maternal and fetal survival were not adversely affected by oral administration to hamsters of up to 1600 mg/kg TDPA on days 6-10 of gestation. No significant differences in the number of soft or skeletal tissue abnormalities were found between treated and sham control fetuses.
Source	:	Food and Drug Research Labs, Inc. (FDRL). (Dec. 29, 1972). Teratologic evaluation of FDA 71-40 (Dilauryl thiodipropionic

acid) in mice, rats, and hamsters. Springfield, VA: U.S. Department of Commerce, National Technical Information Service (NTIS). NTIS publication #PB221 77.

Reliability : This study is assigned a reliability code of 1b according to the criteria established by Klimisch *et al.* (1997). It was not conducted under GLP guidelines but uses methods that generally meet scientific standards, is well documented and is acceptable for assessment.

5.10 OTHER RELEVANT INFORMATION

Type : Metabolism

Method : Dilauryl thiodipropionate was dissolved in corn oil for administering by oral gavage at doses of 107 or 208 mg/kg to Sprague-Dawley rats. When administered in the feed, labeled material was incorporated into powdered Purina Lab Chow, homogenized hen's egg and water to a stiff paste which was heated and formed into sticks of 10-12 grams. Starved male Sprague-Dawley rats were given feed sticks and CO2 collection was started. After 4-8 hr any unconsumed feed was removed and rats were returned to the regular diet. They received 166 mg/kg in the feed.
Urine and CO2 absorbers were processed daily. Liver, kidneys, brain, heart, lungs, whole gastrointestinal tracts and fat samples were removed as sacrifice and frozen with carcasses until assayed. Respiratory CO2 was absorbed in 0.25N or 0125 N sodium hydroxide and counted as BaCO3 on planchets or absorbed in a 1:1 v/v mixture of 2-aminoethanol and 2-methoxyethanol and counted by scintillation spectrometry. Urines and aqueous samples were counted directly with lens paper on planchets, or by addition to a scintillation mixture and counting by scintillation spectrometry. Internal organs were homogenized in acetone after steeping overnight, the acetone extracts were removed and the residues were collected and dried. Residues were assayed by combustion in a Thomas-Ogg apparatus and then counted. Carcasses were autoclaved for 1.5 hr and then homogenized. The slurry was spread out in an unheated forced draft oven for 3 days and the dried material was extracted with hexane for 6 hr. Insoluble material was air dried and placed in a ball mill for 4 days until a fine powder was obtained. Insoluble material and extracts were counted as were tissue insolubles and extracts.

Source : Reynolds, R.C. et al., (1974). The fate of 14Cthiodipropionates in rats. Toxicol Appl Pharmacol 28:133-141.

Ames (1971). The detection of chemical mutagens with enteric bacteria. Chemical Mutagens: Principles and methods for their detection. Vol 1 Chapter 9:267-282.

Bar, F. and Griepentrog, F. (1960). Medizin Ernahr 1:100 cited in BIBRA (1989). Didodecyl thiodipropionate.

FDA (1973). Teratologic evaluation of FDA 71-40 (dilauryl thiodipropionic acid) NTIS PB-223 824.

Food and Drug Research Labs, Inc. (FDRL). (Dec. 29, 1972). Teratologic evaluation of FDA 71-40 (Dilauryl thiodipropionic acid) in mice, rats, and hamsters. Springfield, VA: U.S. Department of Commerce, National Technical Information Service (NTIS). NTIS publication #PB221 77.

Hawley, G.G. (1977). The Condensed Chemical Dictionary, 9th ed. New York: Van Nostrand Reinhold Co.

Klimisch, H.J., Andreae, M and Tillman, U. A systemic approach for evaluating the quality of experimental toxicological and ecotoxicological data. *Regulatory Toxicology and Pharmacology*. 25: 1-5, 1997.

Lehman, A.J. et al., (1951). The pharmacological evaluation of antioxidants. Advances in Food Research. 3:197-208.

Litton Bionetics, Inc (1973) Mutagenic evaluation of compound FDA 71-40, dilauryl thiodipropionic acid. NTIS PB245452.

Maibach, H.I., Gellin, G. and Ring, M. (1975). Is the antioxidant butylated hydroxytoluene a depigmenting agent in man? Contact Dermatitis 1:295-296.

Marhold, J. (1972). Sbornik Vysledku Toxikologickeho Vysetreni Latek A Pripravku, p. 174 Cited in NIOSH RTECS 98-3 (August 1998).

MSDS:Cytec MSDS (9/01/98). Cyanox LTDP Antioxidant MSDS.

MSDS:Hampshire MSDS (3-31-97). Dilauryl thiodipropionate MSDS.

Report on the 13 Week Oral (gavage) Toxicity Study in the Rat followed by a 4 Week Treatment-free Period. Ciba-Geigy Ltd. Basel Switzerland. December 14, 1993.

Report on the Growth Inhibition Test of IRGANOX PS 800 to Green Algae (Scenedesmus subspicatus), Ciba-Geigy Ltd. Basle, Switzerland. September 16, 1992.

Report on the Test for Acute Toxicity of TK10030 to Daphnia Magna, Ciba-Geigy Ltd. Basle, Switzerland. November 25, 1988.

Report on the Test for Acute Toxicity of TK10030 to Zebra-Fish, Ciba-Geigy Ltd. Basle, Switzerland. December 2, 1988.

Report on the Test for Ready Biodegradability of TK10030 in the Modified Sturm Test, Ciba-Geigy Ltd. Basle, Switzerland. February 21, 1989.

Reynolds, R.C. et al., (1974). The fate of 14Cthiodipropionates in rats. Toxicol Appl Pharmacol 28:133-141.

SRI International (1979). Microbial mutagenesis testing of substances; compound report: F76-049, dilauryl thiodipropionate. NTIS report PB89169031.

Syracuse Research Corporation, Syracuse, NY and U.S. Environmental Protection Agency, Office of Pollution Prevention and Toxics (2000)

Tullar, P.E. (1947). The pharmacology and toxicology of thiodipropionic acid and its dilauryl and distearyl esters. Final Report. The Kalusowski Memorial Research Laboratories, School of Pharmacy, The George Washington University, Washington, D.C. Unpublished data. FDA FOIA request #F88-8055. Document #001974-002031.

6. Klimisch Evaluation

Id 123-28-4
Date 01/14/03

Klimisch, H.J., Andreae, M and Tillman, U. A systemic approach for evaluating the quality of experimental toxicological and ecotoxicological data. *Regulatory Toxicology and Pharmacology*. 25: 1-5, 1997.

1 = Valid without restriction

1a: GLP guideline study
1b: Comparable to guideline study
1c: Meets national standard methods (AFNOR/DIN)
1d: Meets generally accepted scientific standards and is described in sufficient detail

2 = Valid with restriction

2a: Guideline study without detailed documentation
2b: Guideline study with acceptable restrictions
2c: Comparable to guideline study with acceptable restrictions
2d: Meets national standard methods with acceptable restrictions
2e: Meets generally accepted scientific standards, well-documented and acceptable for assessment
2f: Accepted calculation method
2g: Data from Handbook or collection of data

3 = Invalid

3a: Documentation insufficient for assessment
3b: Significant methodological deficiencies
3c: Unsuitable test system

4 = Insufficient Documentation

4a: Abstract
4b: Secondary literature
4c: Original reference not yet available
4d: Original reference in foreign language
4e: Documentation insufficient for assessment

EPA Comments on Chemical RTK HPV Challenge Submission:
Thiodipropionates Category

SUMMARY OF EPA COMMENTS

The sponsor, the Thioesters Association, submitted a test plan and robust summaries to EPA for the thiodipropionates category dated December 14, 2001. EPA posted the submission on the ChemRTK HPV Challenge Web site on 15 January 2002.

EPA has reviewed this submission and has reached the following conclusions:

1. Category Justification. The submitter's support for grouping the chemicals under this category is acceptable.

2. Physicochemical Properties and Environmental Fate. All appropriate SIDS-level endpoints have been addressed for the purposes of the HPV Challenge Program.

3. Health Endpoints. All appropriate SIDS-level tests have been performed. EPA agrees that no additional health effects testing is necessary. The submitter needs to address some deficiencies in the robust summaries.

4. Ecotoxicity. EPA agrees that no further ecotoxicity testing is necessary due to the extremely low water solubility and high estimated log K_{ow} values of the category members.

EPA requests that the submitter advise the Agency within 60 days of any modifications to its submission.

EPA COMMENTS ON THIODIPROPIONATES CATEGORY CHALLENGE SUBMISSION

Category Definition

The submitter proposes a category covering three thiodipropionates that are symmetrically esterified by two linear aliphatic groups ranging in size from C_{12} to C_{18}. These compounds are: 3,3'-thiodipropionic acid didodecyl ester (CAS No. 123-28-4), 3,3'-thiodipropionic acid dioctadecyl ester (CAS No. 693-36-7), and 3,3'-thiodipropionic acid ditridecyl ester (CAS No. 10595-72-9).

Category Justification

The submitter's primary justification for the category is based on the expectation that the close structural similarity should result in properties that are either similar or follow a pattern that correlates with changes in the molecular weights of the compounds. The category members are high-molecular weight dithiopropionate esters that differ only in the chain length (C_{12}-C_{18}) of the dialkyl ester functions and are expected to follow a regular pattern for all SIDS-level endpoints. Based on the structures and molecular weights of the category members, as well as available data on category members, EPA agrees that predictive methods and extrapolation and interpolation of data within the category are acceptable. Data provided by the submitter also demonstrate that these compounds generally have mammalian toxicities that are similar (*e.g.*, acute oral LD_{50}, acute irritation thresholds, and genotoxicities) or follow a pattern that parallels changes in molecular weight (*e.g.*, repeated-dose NOAEL).

Justification of the category partly on the basis of similar toxicological properties is supported in the test plan by similar results in acute data available on all three compounds. In addition, genotoxicity assays were negative for the two group members that were tested. The submitter also provided results of acute eye and skin irritation and sensitization studies for the latter two substances, as well as repeated-dose studies. These data indicate similar results for the two compounds. Similar toxicological results are expected for the category members, based on the similarities in structure, size and solubility (especially $\log K_{OW}$ >10), which are properties that directly affect absorption and distribution. EPA agrees that the category is adequately supported based on chemical structure and available data.

Test Plan

Chemistry (melting point, boiling point, vapor pressure, water solubility, and partition coefficient).

All appropriate SIDS-level endpoints have been addressed for the purposes of the HPV Challenge Program.

Environmental Fate (photodegradation, stability in water, biodegradation, fugacity).

All appropriate SIDS-level endpoints have been addressed for the purposes of the HPV Challenge Program.

Health Effects (acute toxicity, repeated-dose toxicity, genetic toxicity, and reproductive/developmental toxicity).

Adequate data are available on the didodecyl ester for all health effects endpoints, on the dioctadecyl ester for acute, repeated-dose and genetic toxicity, and on the ditridecyl ester for acute toxicity only. EPA agrees with the submitter's plan to address data gaps by extrapolation from existing data and that no additional health effects testing is needed.

Acute Toxicity. EPA agrees that no additional acute toxicity testing is needed based on the weight of the evidence for data submitted for all three category members.

Repeated-Dose Toxicity. EPA agrees that no additional repeated-dose toxicity testing is necessary based on the adequate data submitted for 3,3'-thiodipropionic acid didodecyl ester and 3,3'-thiodipropionic acid dioctadecyl ester.

In the test plan (Matrix table, page 2/23 and Table 6, page 16/23), the submitter estimated a NOAEL of ~1125 mg/kg/day for 0.400 kg Fisher rats exposed to 3% 3,3'-thiodipropionic acid dioctadecyl ester in feed for two years. The submitter needs to provide the details of this calculation.

Genetic Toxicity. EPA agrees that no additional genotoxicity testing is needed based on the adequate data submitted for 3,3'-thiodipropionic acid didodecyl ester and 3,3'-thiodipropionic acid dioctadecyl ester.

Reproductive Toxicity. EPA agrees that no further reproductive toxicity testing is needed for the category based on adequate data submitted for 3,3'-thiodipropionic acid didodecyl ester.

Developmental Toxicity. EPA agrees that no additional developmental toxicity testing is needed based on the data for four animal species submitted for 3,3'-thiodipropionic acid didodecyl ester.

Ecotoxicity

Although the submitted test data are inadequate, EPA agrees with the submitter's test plan to conduct no further testing of category members for acute effects because of their extremely low water solubility. In

addition, the high estimated log K_{ow} values for the chemicals preclude the need for chronic ecotoxicity

testing.

Specific Comments on the Robust Summaries

General Comment

The IUCLID data set for 3,3'-thiodipropionic acid dioctadecyl ester did not list the purity of the compound.

The IUCLID data set for 3,3'-thiodipropionic acid ditridecyl ester lists the wrong CAS. No. in the id header on pages 14/37-22/37

Health Effects

Acute Toxicity.

3,3'-Thiodipropionic acid didodecyl ester. The three olive oil vehicle studies did not report the length of the observation period or indicate whether the animals were evaluated for systemic effects aside from mortality.

3,3'-Thiodipropionic acid dioctadecyl ester. The submitter submitted data for four acute toxicity studies (3 in rats and 1 in mice). Information omitted included the gavage vehicle, the length of the observation period, and results for systemic toxicity.

Repeated-Dose Toxicity.

3,3'-Thiodipropionic acid didodecyl ester. The robust summary did not report the gavage vehicle or the specific differences in outcomes following exposure at the NOAEL (350 mg/kg/day) and the NOEL (125 mg/kg/day).

3,3'-Thiodipropionic acid dioctadecyl ester. The robust summary for the 2-year feeding study omitted the animals' sex and incidence data for the observed body weight effects. Also, the summary did not include the submitter's estimation of daily dose (mg/kg/day) that was reported in the test plan (tables on pages 2/23 and 16/23).

Genetic Toxicity.

3,3'-Thiodipropionic acid didodecyl ester. The robust summary for mutation in bacterial cells did not report the positive control or the source of the S9 used for metabolic activation.

The robust summary for the *in vivo* micronucleus assay in rats did not report whether there was any effect on the mitotic index.

3,3'-Thiodipropionic acid dioctadecyl ester. The robust summaries for both studies did not report the source of the metabolic activation system and the purity of the test material.

Reproductive Toxicity. 3,3'-Thiodipropionic acid didodecyl ester. The robust summary did not state the gavage vehicle.

Developmental Toxicity. 3,3'-Thiodipropionic acid didodecyl ester. Robust summaries for all four studies were complete except for the gavage vehicle and the purity of the test substance.

Followup Activity

EPA requests that the submitter advise the Agency within 60 days of any modifications to its submission.